THE ROLE OF OXYGEN IN RETROLENTAL FIBROPLASIA*

BY *Arnall Patz*, M.D.

RETROLENTAL FIBROPLASIA (RLF), first identified by Terry[1] in 1942, within the short span of a dozen years became the largest single cause of infant blindness. In the United States RLF soon exceeded all other causes of blindness in childhood. The incrimination of oxygen as a cause in the early 1950s led to the general practice of strictly curtailing oxygen for the premature infant and the incidence of RLF decreased dramatically throughout the world. It is appropriate to discuss Terry's observations, not only because he properly identified the condition with prematurity, but also because he made the first recorded comment that too much oxygen was one factor to be considered.

Terry's first case[1] was an infant born two months prematurely who at the age of six months presented with a grayish-white membrane filling most of the pupil of each eye. Terry's[2] diagnosis, however, was congenital cataracts, and the patient was admitted to the hospital for a discission operation. Examination under anesthesia was performed, and he reported that "Blood vessels were discovered in the membranes by Doctor P. A. Chandler. Verhoeff, who had seen a similar case the day previously, confirmed the diagnosis of bilateral persistent tunica vasculosa lentis in my case also." Terry[2] then speculated that the abnormal tissue was either "persistence of the entire vascular structure of the fetal vitreous" or "a fibroblastic overgrowth of the persistent tunica vasculosa lentis."

Terry's paper produced some discussion, but no solution to the problem. Terry[3] then embarked upon a meticulous study of the development and regression of the hyaloid artery and tunica vasculosa lentis. He hypothesized that the condition consisted in "primary and secondary changes related to (1) persistence of all or part of the

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hyaloid-artery system; (2) growth of embryonic connective tissue behind the lens; (3) persistence or overgrowth of the fibrillar structure of the vitreous." His study included routinely fixed fetal human eyes and specimens from newborn fetal cats, rats, pigs, and opossums, which had ingested India ink. Stereophotographs made from thick sections gave beautiful three-dimensional reconstructions of the hyaloid artery and tunica vasculosa lentis. From this material he ruled out a persistence of the primary vitreous as contributing to the retrolental mass of opaque tissue, and from his embryological studies of these species he concluded that an overgrowth of embryonic connective tissue in the interstices of the persistent tunica vasculosa lentis behind the lens accounted for the pathology observed. He stated: "It is really a retrolental fibroplasia." This terminology was used in his subsequent reports[4–7] and became generally accepted, although later studies by Owens and Owens[8] showed RLF to be a true retinopathy.

Terry[6] stated that the disease process was not present at birth, but developed from two to six months later. He added: "Many factors have been considered the probable cause of fibroplasia. These include heredity, intraocular inflammation, precocious exposure to light, precocious closure of the ductus arteriosus and the foramen ovale, an increase or decrease of oxygen in the blood, the lower temperature of the premature infants in the incubator in contrast to intrauterine fetal temperature, lack of maternal endocrine environment." Several other deficiencies associated with prematurity were conjectured. Shortly before his untimely death, Terry[6] wrote: "Of all the probable causes listed, precocious exposure to light is considered the most tenable, and preventive measures should be taken." Had Terry lived to continue his studies he probably would have soon discarded the light theory, as did Hepner,[9] 1949, who found that RLF developed in four of five infants who had their eyes shielded from birth. Later, the studies of Crosse[10] and Locke and Reese[11] ruled out light as a factor.

In Terry's seven cases[2] that were presented in detail, comments on oxygen therapy were limited to the first case. He noted that oxygen was started ten minutes after birth and given continuously. On the second day of life oxygen was still being administered. The termination date is not recorded nor are there any other notes on oxygen therapy.

Owens and Owens[8] (1949) were the first to clearly demonstrate that RLF did not result from persistence or abnormality of some part of the hyaloid system with secondary changes in it producing the "fibroplasia." By detailed examinations of infants in the nursery, they found the eyegrounds essentially normal at birth and described the

first detectable abnormality of cases in which classical RLF ultimately developed to be dilatation of the retinal veins. As the condition progressed, the dilatation of the veins became more pronounced, and the arteries became dilated and markedly tortuous. Neovascularization, retinal edema, and hemorrhage followed, with subsequent hemorrhages into the vitreous and ultimate detachment developing.

Friedenwald *et al.*[12] in 1951 first described the capillary endothelial nodular proliferation in the nerve fiber layer of the retina as the primary histopathological lesion in RLF. They stated: "RLF is characterized by the proliferation of the capillary endothelium without normal budding of the capillaries in the nerve fiber layer. Surrounding the capillary proliferation are increased numbers of glial cells. Small areas of edema and hemorrhage may occur in the thickened nerve fiber layer. No inflammatory infiltrates were present. With further progression small pre-retinal and vitreous hemorrhages occur, the newly formed capillaries break through the internal limiting membrane, extend over the surface of the retina and into the vitreous accompanied by a delicate network of fibrous tissue resembling retinitis proliferans."

Reese *et al.*[13] described similar findings in the early pathogenesis of RLF and considered the "spindle cells" noted by Friedenwald and co-workers as "glial cells." In 1954, however, Serpell[14] and Ashton[15] showed that glial-cell proliferation did not occur and that the so-called glial or spindle cells were actually mesenchymal precursors of the developing retinal vessels.

In the late 1940s and early 1950s a host of additional possible causes were added to the list cited earlier by Terry.[4] A detailed discussion of these causes may be found in the survey of Zacharias.[16] Her paper presented an excellent review of the possible etiological agents and summarized the literature up to 1952. The possible causative roles of vitamin E deficiency, adrenal cortical insufficiency, and anoxia received serious consideration.

Owens and Owens,[17] citing the defective fat metabolism of the premature infant, stated: "Of the fat-soluble vitamins, A, D, K and E, the vitamins A and D have been provided routinely and Vitamin K is usually given shortly after birth. Vitamin E alone of the fat-soluble vitamins has not routinely been included." Pointing to the central nervous system lesions produced in vitamin-E-deficient animals and the greater susceptibility to vitamin E deficiency in immature animals, they hypothesized that vitamin E deficiency might be a contributor to

RLF development. To test this concept, they started the following controlled nursery study.

For a period of ten months, alternate infants admitted to the premature nursery of The Johns Hopkins Hospital with birth weights of three pounds (1,360 gm) or less were given supplements of alpha-tocopherol. This was administered by mouth at eight-hour intervals between feedings. "During this 10-month period, eleven infants received Vitamin E supplement and none developed RLF. Fifteen infants in the control group did not receive Vitamin E and five of these developed RLF. We were prevailed upon to shift all infants in our nursery to Vitamin E and to abandon the controlled series." Vitamin E was continued for all infants for approximately a year and a half. In this subsequent period there was no noticeable difference from the previous incidence of the early acute phase of RLF; however, complete membranes appeared in 8 per cent of the infants who had received vitamin E prophylactically, compared to a previous incidence of 22 per cent.[17]

Kinsey[19] (1951) suggested that a higher rate of regression of active disease occurred in infants receiving vitamin E supplements. Within a relatively short period, however, many investigators reported that vitamin E was of no value in either preventing or arresting RLF and its routine administration was gradually discontinued.

The significant difference in RLF incidence between the treated and the untreated groups in the randomized controlled part of the Owens and Owens study has always been puzzling. In re-evaluating their published protocol, now that oxygen has been incriminated, one statement appears important. The treated group of infants received 50 mgm of vitamin E supplement by mouth every eight hours between feedings. A comment about the incubators that were in use at the Harriet Lane Home of The Johns Hopkins Hospital at that time is relevant. Most of the incubators were of the Gordon-Armstrong type. These required opening of the hinged top to gain access to the infant, thereby abruptly lowering the oxygen concentration. The vitamin-E-treated infants, therefore, had the incubator oxygen tension reduced to room air each time the supplement was administered. This drop in oxygen tension could have had an important protective effect on oxygen-induced retinal damage and may explain the initial promising results with vitamin E therapy.

During late 1949 and early 1950, many nurseries started acquiring the Isolette type of incubator. This permitted the administration of

medication and actual feeding through sleeves in the wall of the incubator so that the oxygen concentration was not reduced when the infants received vitamin E supplements. Since many hospitals had combinations of the older type of incubators as well as Isolettes, it is conceivable that this explains why the experiences of other nurseries in the 1950–1 period failed to confirm the original findings of Owens and Owens.

Reese[20] in 1951 suggested that a deficiency of adrenal cortical hormone might be responsible for the angiomatous process of early RLF. It was thought that the administration of ACTH or cortisone might inhibit the vascular proliferative stages of RLF. Reese's initial results with therapeutic administration of these hormones were quite promising and suggested that an effective agent had been discovered to prevent and arrest RLF development. Shortly thereafter a large number of investigators reported that ACTH and cortisone were ineffective and in 1952 Reese *et al.*[21] concluded that these hormones had no effect on the course of RLF and discontinued their use.

A large number of papers suggested that simple anoxia or the relative anoxia that follows sudden lowering of the oxygen tension of an oxygen-acclimatized infant was the cause of RLF.

Ingalls[22] (1948) suggested that sublethal oxygen lack (resulting perhaps from antepartum hemorrhage, placenta praevia, or eclampsia) leads to permanent damage of vascular tissue. Ingalls and co-workers[23] (1952) produced the "open eye" syndrome in the offspring of mice subjected to an anoxic insult during pregnancy and suggested that the pathology might be similar in some respects to that seen in retrolental fibroplasia. The interesting ocular abnormalities, however, did not show the proliferating endothelial nodules in the retina that are characteristic of RLF.

Szewczyk[24] (1951) in his preliminary report, states: "It is believed that RLF is due simply to subclinical anoxia during a period of time when the incompletely developed retina utilizes oxygen at a rapid rate." He noted that as long as premature infants were kept in oxygen there was no evidence of vascular dilatation, tortuosity, or edema. Changes, however, began in twenty-four to forty-eight hours, without exception, in seven infants removed rapidly from oxygen incubators. Szewcyzk noted that RLF did not develop in infants who had an average stay of 20 days in incubators, whereas it did develop in those who stayed for an average of 30 days. He stated: "It became apparent that the group of children who developed RLF were actually more oxygen deficient than the others," and "it was noted that, as a rule, the

apparently normal premature infant, while in oxygen, had retinal vessels, either small or attenuated in caliber (frequently thread-like) which were not tortuous." Szewczyk further stated that normal premature infants "as a rule were noted to have vessels which could be called full or engorged." It is now apparent that this stage of engorgement probably represented the first change that occurs when the subject is removed from oxygen or when the oxygen tension is significantly lowered from a high level.

He reported that nine patients with early retrolental fibroplasia, all of whom had marked vascular tortuosity and neovascularization, showed immediate improvement on placing them under high oxygen tension. Within twenty-four hours a dramatic constriction in the previously dilated vessels was noted. This observation is quite valid in the light of our present knowledge and demonstrates the severe vasospastic effect of high oxygen on abnormally dilated vessels in early RLF as well as on those of normal caliber. Animal data, however, suggest that although the larger vessels will constrict with oxygen, vasoconstriction may result in damage to smaller vessels.

Szewczyk[25] (1952) concluded that RLF may be caused either by inadequate oxygenation or by exposing an infant to a high concentration of oxygen and then withdrawing it so rapidly that acclimatization cannot take place before irreparable damage is done from relative anoxia. This latter part of his statement is consistent with our present state of knowledge. It is apparent that Szewczyk was observing the secondary reaction of vasodilatation and tortuosity that follows the initial oxygen exposure. Recent studies from our laboratory show that kittens treated initially with oxygen and removed to room air for 72 hours, to allow time for dilatation and tortuosity to develop, will then show a significant constriction of the vessels when placed back in oxygen for two hours.[26]

Jefferson,[27] in a retrospective study of the RLF cases in a hospital in Manchester, England, reported in August 1952 that the only factor common to these cases, with one exception, was the use of oxygen tents. He suggested that RLF develops "when the tension of oxygen available to the tissues of the premature infant is suddenly lowered." Following Szewczyk's suggestion, infants with early RLF were treated with oxygen. He noted that "the vascular engorgement disappeared within forty-eight hours, capillary tufts ceased to be visible and retinal edema subsided."

Rudolph and Sirlin[28] (1951) suggested that anoxia was either the principal factor or an important contributory factor in the pathogenesis

of RLF. Klien[29] (1949), from histopathologic studies of RLF cases, suggested that anoxia may play a role in RLF. By mid-1952, a large number of reports had appeared suggesting that RLF was due directly to anoxia or due to a "secondary" anoxia that occurred on the removal to room air of an infant previously acclimatized to high oxygen concentrations.

Kinsey and Zacharias[30] (1949) reviewed the hospital records from several institutions in the United States and reported the following: "Examination of the hospital records showed that the treatment of the infant varied significantly with time in three respects only:—first, administration of a multiple vitamin preparation in which the fat-soluble vitamins are made miscible with water; secondly, administration of iron in greatly increased quantities and thirdly, more frequent administration of oxygen." These authors further stated that "infants in whom RLF subsequently developed remained in the nursery, water jacket incubator and in oxygen for longer periods than infants in whom RLF did not develop," and that "this suggests that the general health of the infants in whom RLF subsequently developed may have been poorer than of those whose eyes remained normal or possibly that the latter were larger infants requiring a shorter stay in the hospital." Their survey showed that the average period in oxygen for normal infants was twelve days, whereas for those with RLF it was twenty-one days.

Gordon[31,32] noted that a high incidence of RLF in Denver, Colorado, coincided with the transferral of the premature nursery "to new quarters in which the piping in of oxygen from a central supply had made it as easily available as water from a faucet." A reduction in RLF incidence occurred when oxygen tensions in the incubator were lowered. LeLong *et al.*[33] (1951) speculated that hyperoxygenation might contribute to RLF: "Further cooling and anoxia at birth have been accused. On the contrary, we have reason to ask ourselves if not hyperoxygenation might be responsible. It is essential to define more strictly the indications for oxygen and to administer it more carefully."

Campbell[34] in 1951 reviewed the records of three Melbourne (Australia) hospitals. She compared the incidence of RLF in the nurseries of these three hospitals. "In Institution I cost of oxygen was not a limiting factor and it was given liberally both for prophylaxis as well as for treatment of cyanosis. Institution II used a moderate amount of oxygen and cost was not a factor. Institution III consisted of private patients. Here, cost was a consideration. Oxygen was therefore used with more economy." In a retrospective analysis of the period from 1948 to 1950, she found a significantly lower incidence of RLF in the private patients from Institution III when compared with Institution I

where oxygen was given more liberally. Campbell, pointing to the normal hypoxic condition *in utero*, stated: "Thus within a very short space of time the hypoxic fetus becomes the infant with a higher oxygen environment to his cells." Although her study was retrospective and had no controls, it represented the first published report with clinical data to consider increased use of oxygen as the causal agent in RLF.

Ryan[35] (1952) had examined many of the cases referred to in Campbell's paper.[34] In March 1952 he stated that no case of RLF had occurred at the Woman's Hospital in Melbourne, Australia, prior to the introduction of "a most efficient oxygen cot." With this apparatus "it was the practice of the nursery staff to give oxygen liberally to all babies even when apparently not requiring it." Twenty-one of twenty-three cases of RLF identified in Melbourne occurred at the Woman's Hospital, and in October 1950 it was decided that oxygen would be restricted to clinical need in view of the suspicions about it as a possible cause of RLF. No further cases had been recorded in the nursery at the time of his report.

Goldman and Tobler[36] (1952) stated that no RLF occurred in 570 consecutive premature infants until 1951 when the first case was detected. This infant was raised in the Isolette incubator and received high concentrations of oxygen. They postulated that "(1) the unphysiological effect of the high oxygen intake may either cause direct damage or (2) the premature may have acclimatized to the excess oxygen and becomes ill when rapidly weaned from the higher oxygen atmosphere," and therefore concluded: "Definitely a restriction of the amount of oxygen given to premature infants is necessary."

Crosse and Evans[37] (1952) comparing the incidence of RLF in British cities and nurseries using different oxygen routines, found that, in general, where oxygen was limited that the incidence of the disease was lower. Also, in one hospital little oxygen was given prior to 1948 and the incidence of RLF was only 3 per cent. In 1949 and 1950 much oxygen was used and the incidence rose to 19.2 per cent. From July 1950 to July 1951 oxygen was used minimally and the incidence of RLF dropped to zero per cent. Crosse and Evans concluded: "We are of the opinion that the real source of this disease lies in the widening and prolonged use of a high concentration of oxygen in the early life of the premature infants of low birth weight."

Several papers appeared which seriously questioned the concept that excessive oxygen was related causally to RLF. Bembridge and Houlton[39] reported that because the use of high oxygen tensions

appeared to correlate with an upsurge in RLF incidence in Oxford, England, the oxygen concentrations were lowered in his nursery. Cases continued to occur after the reduction of oxygen tension had taken place. In 1952 Bembridge *et al.*,[40] stated: "One baby in our series who had received no oxygen developed the disease and in other centers where oxygen is used freely no cases have occurred." Zacharias,[16] in her comprehensive review published in October 1952, stated: "At present no strict correlation appears to exist between the use of oxygen and either the presence or absence of retrolental fibroplasia. Instances of most of these combinations can be found. For example, there has been a high incidence of the disease at the Boston Lying-In Hospital, the New York Hospital and an Australian hospital, where there has been a liberal use of oxygen, and there are no cases at the New Orleans Charity Hospital and some centers in England where oxygen is also used freely. . . . The fact remains that there are examples of hospitals where incidence has risen while the method of oxygen treatment has remained unchanged." "This controversy," she concluded, "must be eventually resolved by well-controlled clinical experiments."

The first controlled nursery study to test the high oxygen theory was reported by Patz *et al.*[41] in 1952, one month before the appearance of Zacharias' review. "Starting in January 1951 infants were placed into either a high or low oxygen routine on a random basis and not according to birth weight or other clinical indications. Infants in high oxygen were maintained at these levels constantly for from four to seven weeks. Infants in low oxygen were kept in incubators for from 24 hours up to two weeks at levels under 40%." At the end of the first year, seven of twenty-eight infants in the high-oxygen group had advanced RLF. No cases of advanced disease occurred in thirty-seven infants in the low-oxygen group. The severe vasoconstriction in the premature retina as a specific response to hyperoxia was discovered and its possible role in the pathogenesis of RLF was discussed. A significant narrowing of the retinal arteries and veins was recorded after one hour of exposure to 80 per cent oxygen in several premature infants. Four infants who ultimately had advanced RLF had "marked attenuation of their retinal vessels occurring prior to the development of dilatation and tortuosity." It was suggested that increased oxygen tension by causing severe vasoconstriction could diminish the supply of metabolites other than oxygen to the premature retina. It was further suggested that high oxygen might alter enzyme systems in the premature retina causing damage (Figure 1).

The first animal experiments to demonstrate ocular damage on the

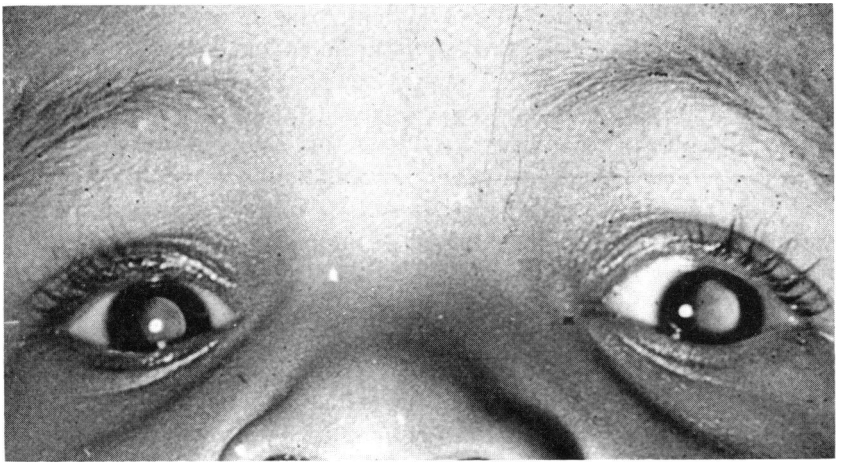


FIGURE 1

Stage 5 RLF. Case in our nursery that called attention to oxygen by having a funnel over mouth for added oxygen while in incubator.

immature eye from increased oxygen were recorded by Gyllensten and Hellström[42] of Stockholm in November 1952. Newborn mice with immature eyes were exposed to 100 per cent oxygen intermittently for one to three weeks. Approximately 50 animals were subjected to this oxygen régime and the most consistent findings were "hemorrhages in the vitreous body and behind the lens and into the anterior chamber, hyperplasia of the tunica vasculosa lentis, detachment of the optical retina from the pigment layer with multiple retinal folding and, in some cases, a vascular and cellular tissue with fibrillary elements formed in the vitreous body." Endothelial nodules in the retina and proliferating capillary tufts into the vitreous were not recorded in their original paper.

Ashton *et al.*[43] of London reported in September 1953 that marked vasoconstriction and obliteration of the retinal vessels of the young kitten occur during hyperoxia. The severe retinal vasoconstrictive response to oxygen in the premature infant had been previously reported, but Ashton and his co-workers, using flat retinal preparations injected with India ink, demonstrated for the first time that obliteration of the retinal vessels occurs in prolonged hyperoxia and that it was "directly proportional to the degree of immaturity of the retinal vascularization, to the duration of exposure to oxygen and to the degree of oxygen concentration." Further, that "while the basic injury of

vascular obliteration is inflicted in high oxygen concentrations, the effect of this oxygen is not evident until the animal returns to ordinary atmospheric conditions." One animal which was returned to air for eighteen days following an initial oxygen exposure showed proliferating capillary tufts extending from the retina into the vitreous. Thus, both the primary vasoconstrictive and obliterative response to oxygen and the later secondary vasoproliferations following removal to air were demonstrated in an experimental animal.

In November 1953, Patz *et al.*[44] published their animal observations. "Paralleling the nursery study begun in 1951, an extensive investigation was started to evaluate both the ocular and systemic effect of oxygen on several species of animals." The characteristic endothelial nodules in the nerve fiber layer of the retina with the budding of new vessels through the internal limiting membrane into the vitreous was reported in newborn mice, kittens, and puppies raised in oxygen.

In 1954 Gyllensten and Hellström[45] found classical capillary tufts budding into the vitreous in mice subjected to hyperoxia and then removed to air for ten days. These combined animal studies conducted independently in three different laboratories gave strong support to the clinical studies implicating oxygen in RLF. Experimental animal studies were continued independently in these three laboratories during the next several years.

In May 1954 Lanman and co-workers[46] reporting on the second controlled nursery study on oxygen therapy, noted that "irreversible, cicatricial RLF appeared in infants in the group with high oxygen but not in the group with low oxygen. Reversible vascular stage lesions occurred in both groups but with nine times the frequency in the group with high oxygen concentration." It was especially significant that the mortality rate, except for deaths due to recognized causes bearing no relationship to oxygen therapy, was the same in the high- and low-oxygen groups.

Kinsey[48] made a co-operative hospital study on oxygen therapy involving eighteen participating hospitals in the United States. He reported that "of the factors considered, the controlled study shows conclusively that the length of time the premature infant is kept in an oxygen-enriched environment is an important factor in the production of RLF."

Gordon[32] (1954) explained some reasons for the extensive use of oxygen in the care of the premature infant that had come into general usage in the late 1940s: "With decreases in mortality from infection, there has been increasing emphasis on deaths in the first days of life

because of respiratory failure. Small premature infants have marked handicaps in respiration. They may have poor gag and cough reflexes, under-developed capillaries in the lungs, medulla and other tissues, sparse elastic tissue in the lungs. They are more seriously damaged by perinatal factors which lead to anoxia. They have spontaneous attacks of apnea, irregular respiration in room air, the latter two items being considered manifestations of defective neural or humoral control of respiration. These considerations and the increased availability of incubators have led to an extensive routine use of oxygen in the care of premature infants during the first few days of life."

By the mid-1950s abundant clinical and experimental data had accumulated showing that RLF was due to the overuse of oxygen and that a careful curtailment in oxygen reduced dramatically the incidence of retrolental fibroplasia throughout the world. Most ophthalmologists and pediatricians considered the issue settled, especially since there appeared to be no adverse effect on mortality by oxygen restriction in the presence of cyanosis.

In the early 1960s several reports appeared in the pediatric literature concerning infants with pulmonary disease, especially the "respiratory distress syndrome." An epidemiological approach by Avery and Oppenheimer[49] showed a higher mortality in premature infants cared for from 1954 to 1958, when oxygen was curtailed, compared with the previous period of 1944 to 1948, when it was used liberally. Although these investigators did not claim that oxygen curtailment was principally responsible, it is significant that oxygen restriction was the chief difference in management during these two periods. Recent studies by Strang and MacLeish[50] (1961), Warley and Gairdner[51] (1962), and Prod'ham *et al.*[52] (1965) have documented the severe oxygen deprivation in infants with the respiratory distress syndrome. Approximately 40,000 premature infants are afflicted with this syndrome in the United States alone. The mortality rate has been approximately 50 per cent in these infants and at autopsy they show "hyaline membrane disease."[53]

The pendulum which swung in the 1950s toward a rigid curtailment of oxygen to prevent RLF may swing back as the need for high oxygen for the respiratory distressed infant becomes more abundantly documented. Many investigators today are seriously concerned that a resurgence of RLF cases may occur with any liberalization of oxygen usage without proper monitoring and safeguards for the infant.[54,55] Frequent sampling of arterial blood-oxygen levels provides a means of avoiding potentially retinotoxic oxygen levels. Unfortunately, there are no data

available on the precise arterial pO_2 values that cause retinal damage. Furthermore, the technique of arterial sampling requires a highly skilled pediatric team and the blood oxygen analysis needs specially trained technicians and expensive instrumentation. For these reasons only a very small number of hospitals are equipped today to monitor arterial oxygen tension.

Since arterial oxygen monitoring is not readily available in the majority of hospitals, the ophthalmologist may make an important contribution to safer oxygen therapy. Examination of the retina for retinal vasoconstriction can provide a general guideline to the arterial oxygen levels that have been maintained. The retina is the main target of concern from excessive arterial pO_2 levels. Therefore, ophthalmoscopy should be performed, where feasible, whenever the premature infant receives prolonged high concentrations of oxygen. If the blood level has been excessive, the premature retina will frequently show a proportional degree of vasospasm. Prompt reduction in oxygen at this time may prevent irreversible retinal vessel damage.[55]

Since approximately 40,000 premature infants are afflicted annually with the respiratory distress syndrome in the United States alone, new research is urgently needed to establish safer guidelines for oxygen therapy to the premature infant.

NURSERY STUDIES

Three controlled nursery studies in which oxygen was administered liberally or restrictedly on a random basis and not according to birth weight or clinical need have been reported. The details of these studies will be omitted here except for certain aspects that relate to current problems of oxygen therapy for the "respiratory distress syndrome."

Our own nursery studies[41] can be summarized in Figures 2 and 3. Figure 2, a retrospective analysis of RLF cases from January 1948 to January 1951, shows a strong association between the number of days' exposure to oxygen and the incidence of RLF. From these results, high-oxygen therapy could not, however, be accepted as a causal factor, since the smaller infants generally received more oxygen. A controlled study was instituted in January 1951 to test the role of oxygen therapy. Infants were placed into either a high- or low-oxygen regime on a random admission basis. Infants in high oxygen were maintained at 65 to 70 per cent oxygen levels for four to seven weeks, whereas infants in the low-oxygen group either received no added oxygen, or, if given oxygen, received it in a concentration of less than 40 per cent.

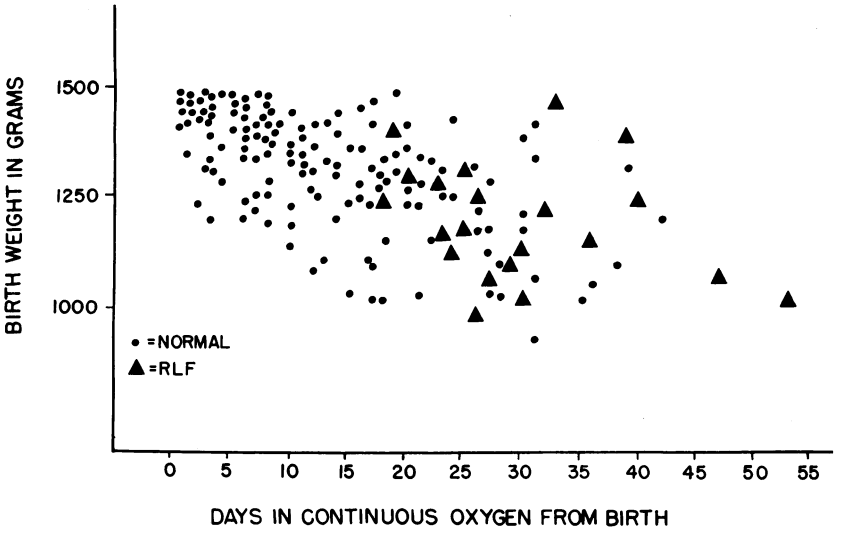


FIGURE 2

RLF cases in our nursery from 1948 through 1950. Note the association between number of days in oxygen and RLF incidence. (Uncontrolled data from D.C. General Hospital.)

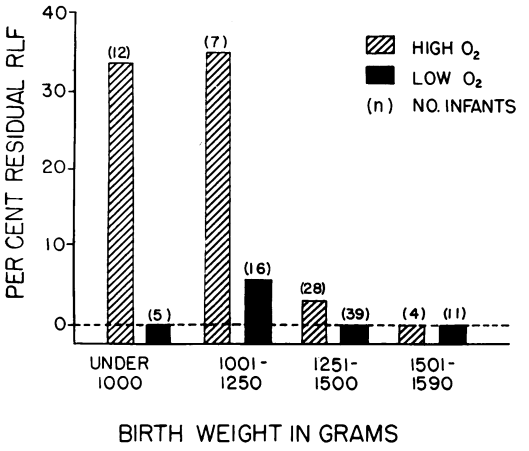


FIGURE 3

Data from controlled nursery study, January 1951 through May 1953. Note striking difference within each weight group of RLF incidence.

The controlled study is highly significant with a chi^2 of 1.44 and a p value of 0.01. The one infant with RLF in the low-oxygen group had received oxygen at 35 to 40 per cent concentration for ten days. The controlled study of Lanman and co-workers[46] and the co-operative hospital study of Kinsey[48] showed similar results. Several non-randomized studies cited in the introduction gave further confidence to the role of oxygen in RLF.

In our own study no significant difference in mortality was noted in the high- and low-oxygen groups. However, 120 infants is a relatively small number on which to base meaningful conclusions about mortality rate. Furthermore, infants in the low-oxygen group had oxygen given for up to two weeks whenever there was cyanosis, save that the concentration of oxygen was always kept under 40 per cent. In the Lanman study the mortality rate was 20 per cent in the group with high oxygen and 30 per cent in the low-oxygen group. The difference between these percentages was not considered statistically significant. Moreover, five infants in the group with low-oxygen concentration, according to the authors, "died after the age of 10 days from known causes which we feel cannot reasonably be attributed to the differences in oxygen therapy." Excluding those five infants the mortality becomes 20 per cent for each group. Here again the number of cases was relatively small—64 infants, 36 in the high group and 28 in the low group.

The co-operative hospital study of Kinsey,[48] which involved 786 infants, is sufficiently large to give more meaningful data on mortality. It showed that the reduction of the length of stay in oxygen to that deemed necessary to meet the acute clinical needs of the infant does not affect mortality. Since only infants who survived for forty-eight hours were admitted to the co-operative study, these mortality figures become less meaningful in consideration of oxygen treatment during the first two days of life, a period frequently critical for the respiratory distressed infant. Furthermore, unrestricted oxygen for forty-eight hours in an infant not requiring oxygen may increase RLF risk.

CLASSIFICATION OF RETROLENTAL FIBROPLASIA

Reese *et al.*[57] classified retrolental fibroplasia into five active stages and five corresponding cicatricial stages. The reader is referred to their excellent paper illustrating this classification which has been generally adopted. Their description was prepared, however, prior to the incrimination of oxygen as a cause of RLF. Our nursery studies,[41] and the independent findings of Huggert,[58] showed that the initial appearance of the retinas prior to development of stage I of the standard classifica-

tion is a severe constriction and attenuation of the vessels. Rather than suggest the revision of the classification that has been generally adopted, we have recommended that the stage of persistent severe retinal vasoconstriction be classified as "preretrolental fibroplasia." This is followed by stage I which consists of dilatation and tortuosity of the vessels with localized areas of neovascularization and retinal edema.

RETROLENTAL FIBROPLASIA WITH NO OXYGEN THERAPY

In the early 1950s the report of an occasional case of RLF occurring where the infant received little or no supplementary oxygen was the main cause for scepticism in accepting the overuse of oxygen as the cause of the disease. There have been rare instances of RLF occurring without use of supplemental oxygen. In my own files on 104 documented cases of cicatricial RLF where I had personally either examined or had access to the record of the patient, there is one instance of an infant who had no known supplemental oxygen. Within the oxygen theory it is reasonable, however, to explain these rare cases.

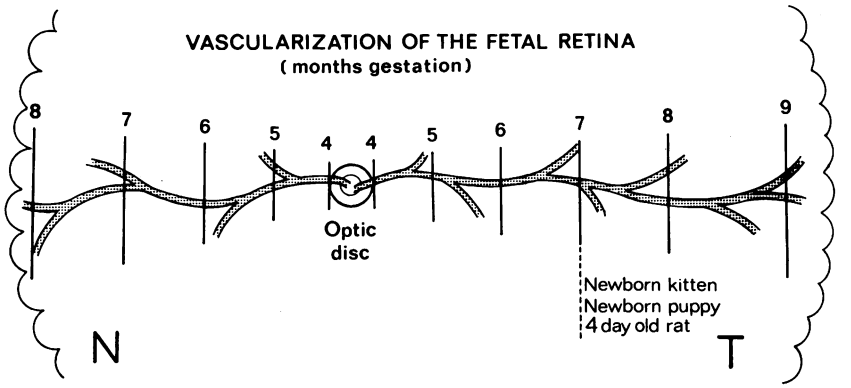


FIGURE 4

Schematic diagram showing retinal vascularization of the human fetus. Note that the nasal periphery is completely vascularized at eight months gestation whereas the temporal periphery is not fully vascularized until after term.

In utero the fetus is relatively cyanotic as the arterial oxygen saturation is appreciably lower than in the normal infant after birth while breathing room air. *In utero* there is a normal admixture of the venous and arterial blood through the patent foramen ovale and ductus arteriosus. After birth the arterial saturation in the normal premature

infant rises rapidly as the lungs expand and the ductus and the foramen ovale close. The hemoglobin saturation and arterial pO_2 rise significantly after birth even in room air without added oxygen. One might postulate that in a sensitive premature retina this sudden rise in retinal arterial pO_2 leads to irreversible constriction and vaso-obliteration thereby explaining the occasional case of RLF developing without added oxygen. One might also, however, raise the possibility that these rare cases of RLF without oxygen may have resulted from as yet undetermined causes.

RETROLENTAL FIBROPLASIA IN FULL-TERM INFANTS

According to the earlier studies by Mann[61] the retina is fully vascularized at eight months' gestation. From this concept it would be impossible to explain the development of RLF in the full-term infant on the assumption that only the incompletely vascularized retina is susceptible to oxygen and to RLF (Figure 5). In 1957, I examined

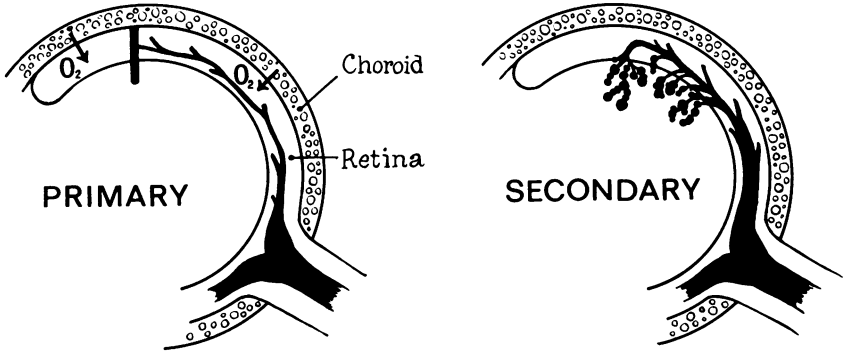


FIGURE 5

Schematic representation of the effect of oxygen on the immature retina. During the primary stage, there is vasoconstriction, obliteration, and damage to endothelium. The secondary stage is vasoproliferation and dilatation of surviving larger vessels.

cross-sections of the retinas of two stillborn full-term infants and discovered that the temporal periphery was completely devoid of vessels. I suggested that the occasional situation where the retina was incompletely vascularized could explain these rare cases in full-term infants.[62] Cogan,[63] however, utilizing the trypsin digestion technique found that the retina normally is incompletely vascularized temporally even in the full-term infant and that this anterior temporal portion becomes fully vascularized during the first days of life. Thus, we have

a ready explanation for RLF occurring even in the full-term infant and, furthermore, these data indicate that even for the full-term infant oxygen should be administered cautiously and should be curtailed to specific clinical needs and not given indiscriminately.

The greater predilection for retrolental fibroplasia to involve the temporal quadrant of the retina also supports the basic premise of oxygen susceptibility of immature retinal vessels, since the anterior zone of the temporal periphery is the last portion of the human retina to become completely vascularized. In our own experience,[64] and in that of Reese and Stepanik,[65] when RLF involves only one quadrant, the temporal periphery is usually involved.

RATE OF WITHDRAWAL FROM OXYGEN

Several investigators have suggested that gradual withdrawal from oxygen minimizes the retinal damage induced by hyperoxia. This concept is quite logical from a strict physiological point of view of acclimatization; however, one must always weigh the possibility that during the period of gradual withdrawal added oxygen during the period of withdrawal may cause additional obliteration and damage to the retinal vessels. Animal experimentation in our laboratory[66] and by Gyllensten and Hellström[67] failed to show any protective effect from gradual withdrawal. These experiments in mice may not be exactly comparable to the human problem, however. The only controlled nursery study on rate of withdrawal is by Bedrossian and co-workers[68] (1954) who reported a significantly higher incidence of RLF in infants rapidly removed from an atmosphere of continuous oxygen as compared with a group where oxygen was gradually reduced. Their results, however, may have resulted from the "gradual withdrawal" group receiving only 50 per cent oxygen initially whereas the "rapid withdrawal" infants were first treated with 60 per cent oxygen. The co-operative study of Kinsey[48] showed that the incidence of RLF appeared to increase with each additional day of exposure to oxygen. Although the question has never been satisfactorily answered, there appears to be insufficient evidence to justify "gradual withdrawal" when weighed against the possible risk of the added stay in oxygen causing further retinal vessel damage.

EXPERIMENTAL STUDIES

The effects of oxygen on the immature retina with special emphasis on the problem of retrolental fibroplasia have been investigated independently by Ashton and co-workers, Gyllensten and Hellström, and

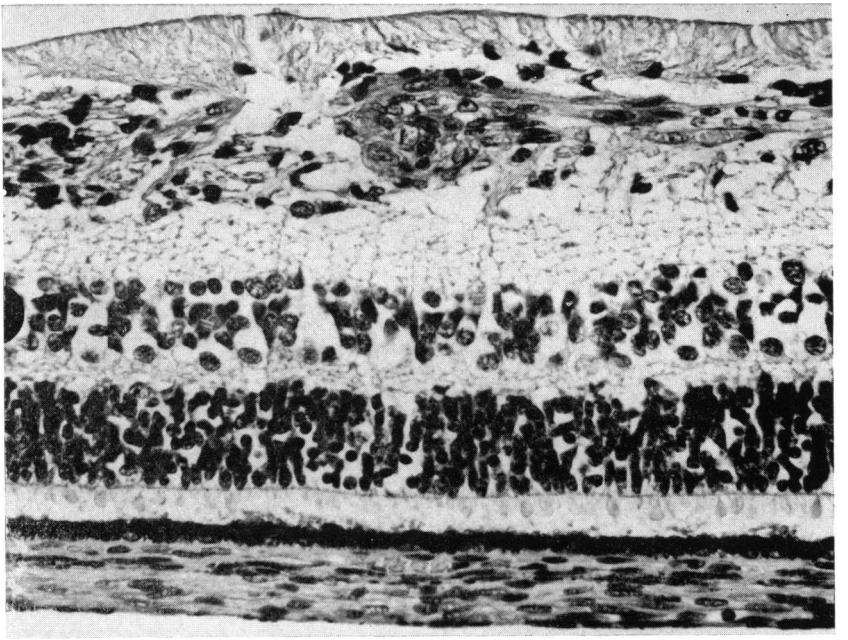
in our own laboratory. These earlier observations will be only briefly summarized here since they have been reported in detail in the British, Swedish, and American literature. The pioneer studies on the development of the retinal vessels by Michaelson[69] served as a useful background to these studies, and Campbell[70] provided the first clear demonstration that oxygen tension could influence the degree of retinal capillary growth.

The animal experiments on RLF, using kittens and mice, generally demonstrated that exposing animals with incompletely vascularized retinas to elevated oxygen tensions can lead to the development of the classical changes seen in early human retrolental fibroplasia. These studies showed that the animal retina is sensitive to oxygen injury only when the retinal vasculature is incomplete (Figure 4). When animals were permitted to mature to the stage when the retina was fully vascularized, no retinal vascular lesions resulted from exposure to hyperoxia. Further, it was generally observed that the degree of susceptibility to oxygen-induced injury was inversely proportional to the degree of vascularization of the developing retina. The severity of lesions produced was found to be directly proportional to the duration of oxygen exposure and to the concentration of oxygen administered.

The effects of oxygen on the immature retina can be conveniently divided into two stages. The primary stage, or vasoconstrictive and obliterative phase, occurs during the exposure to hyperoxia and there is also a suppression of the normal anterior-ward vascularization of the retina. The secondary stage, or vasoproliferative phase, typically follows removal from oxygen to room air, and involves dilatation and tortuosity of the surviving larger vessels with neovascularization and proliferation of new vessels into the vitreous (Figures 5–9).

Ashton and Pedler[71] (1962), studying the primary effect of hyperoxia on the kitten retina by digest preparations and electron microscopy, demonstrated a selective cytotoxic injury to the endothelial cells by hyperoxia. These observations were subsequently confirmed in our laboratory[72] (Figure 10).

The mechanism of the severe vasoconstrictive response of the immature human and animal retina has remained unexplained. I found,[73] as did Ashton *et al.*,[74] that CO_2, normally a potent vasodilator, had no effect on the oxygen-induced vasoconstriction. I found that sympathectomy in dogs[73] had no effect and Cook and Ashton[75] confirmed this in kittens. None of the usual vasodilators had any effect.[73,74] Ashton and co-workers[74] found less vaso-obliteration in one group of kittens



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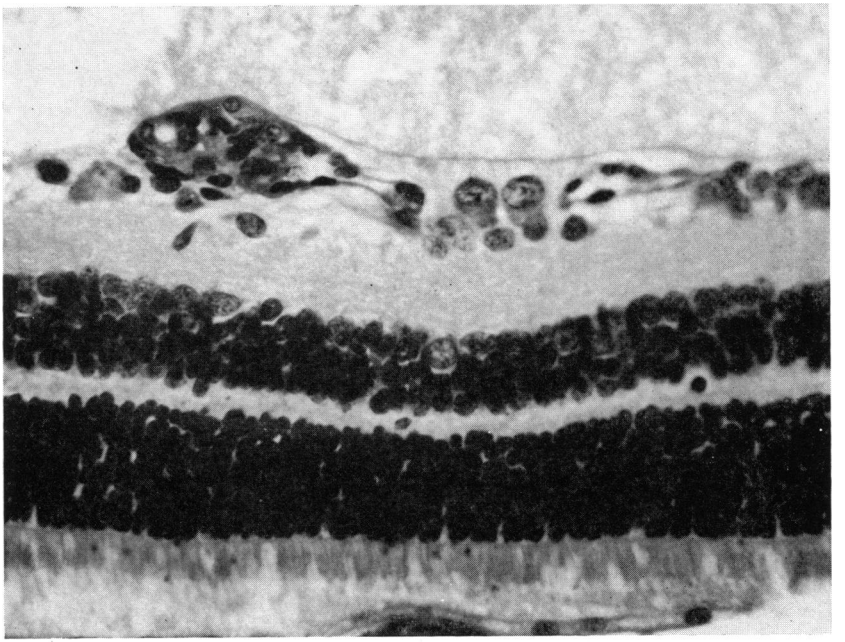
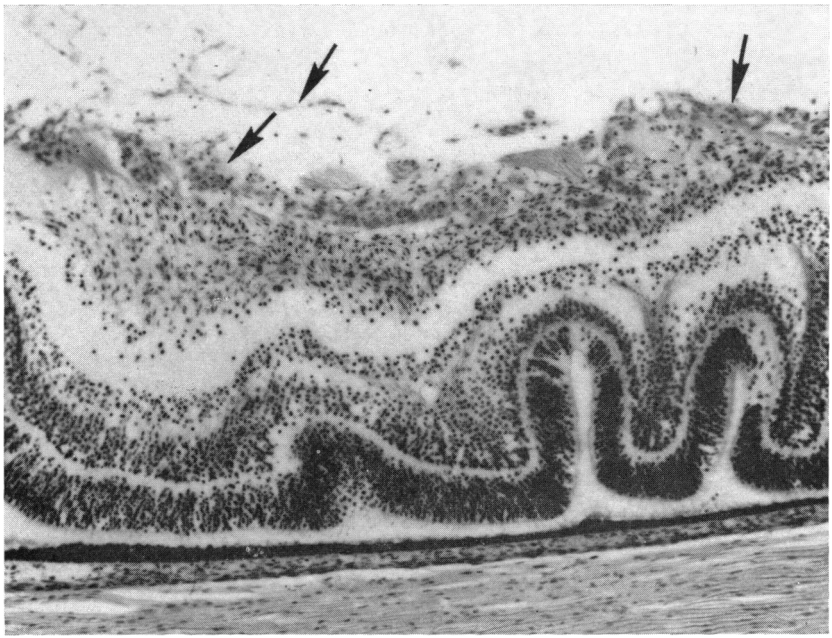


B

FIGURE 6

A, section from infant dying with early RLF; arrow points to typical proliferating endothelial nodule first described by Friedenwald *et al.*[12] B, endothelial nodule (arrow) proliferating through internal limiting membrane in 21-day-old mouse exposed to hyperoxia; this was our first experimental RLF nodule.[44]



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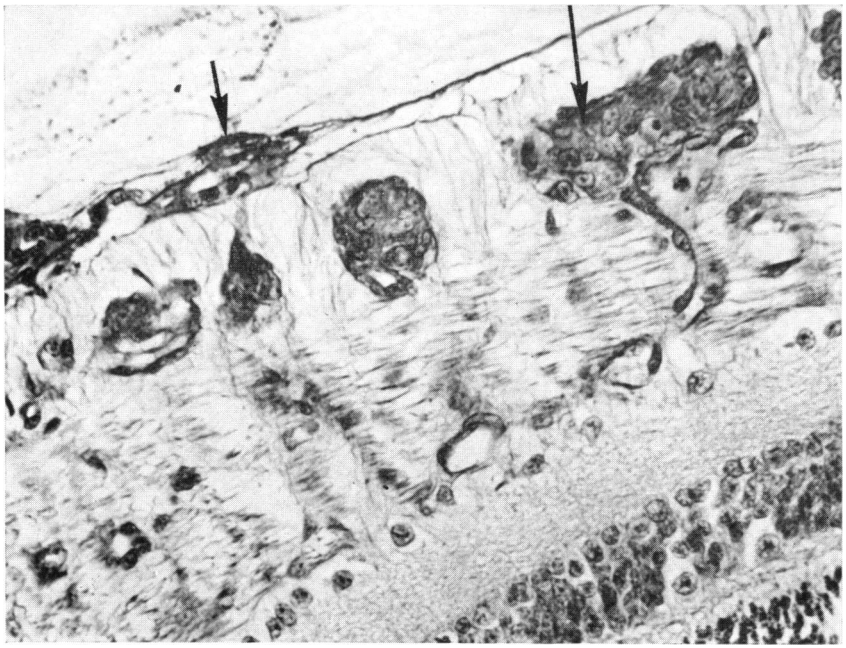


B

FIGURE 7

A, anterior portion of retina from infant in Figure 6A; arrows point to neovascularization on retinal surface and in vitreous. B, section from 21-day-old kitten exposed to 70 per cent oxygen for the first four days of life, and then transfered to room air; short arrow points to neovascularization on surface of retina and long arrow to nodule in nerve fiber layer; note that deeper capillaries are normal.

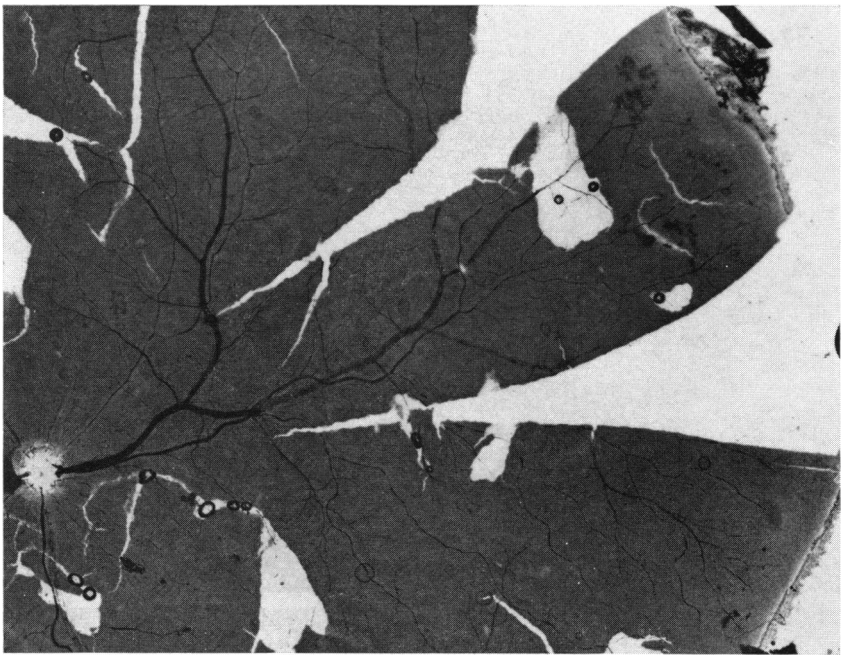
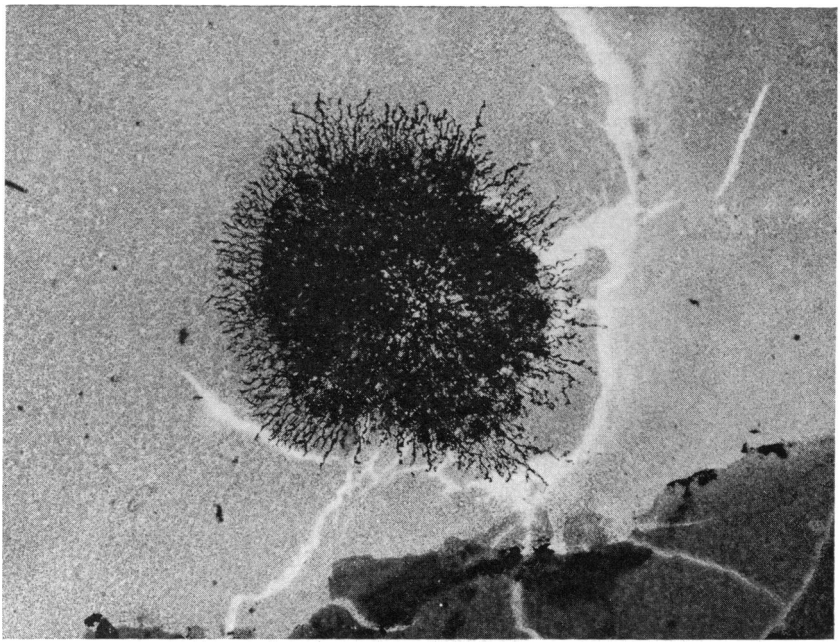


FIGURE 8
India-ink-injected flat preparation of 21-day-old normal kitten raised in room air showing retina vascularized to the ora.

treated with anticoagulants; however, these studies were apparently not pursued.

In the studies of Patz *et al.*[44] vasoproliferations could be observed in several animals who were kept in continuous high concentrations of oxygen until sacrificed. The occurrence of vasoproliferation in animals while in prolonged exposure to oxygen is consistent with the observation of twelve infants in our nursery,[56] and of eleven infants followed by Day,[56] who developed the early vascular proliferative lesions of RLF while still in continuous oxygen in the incubator. These findings were in contrast to those of others, however.[76,74]

Even though frank pulmonary damage was not apparent in our early animal experiments and was not clinically recognizable in our nursery study, it is conceivable that subtle changes in the lungs had developed, similar to those documented in pulmonary oxygen poisoning. These could have caused a significant lowering of the arterial oxygen tension in the eye even though the animal or infant was still breathing oxygen. This change could explain, within the theory of



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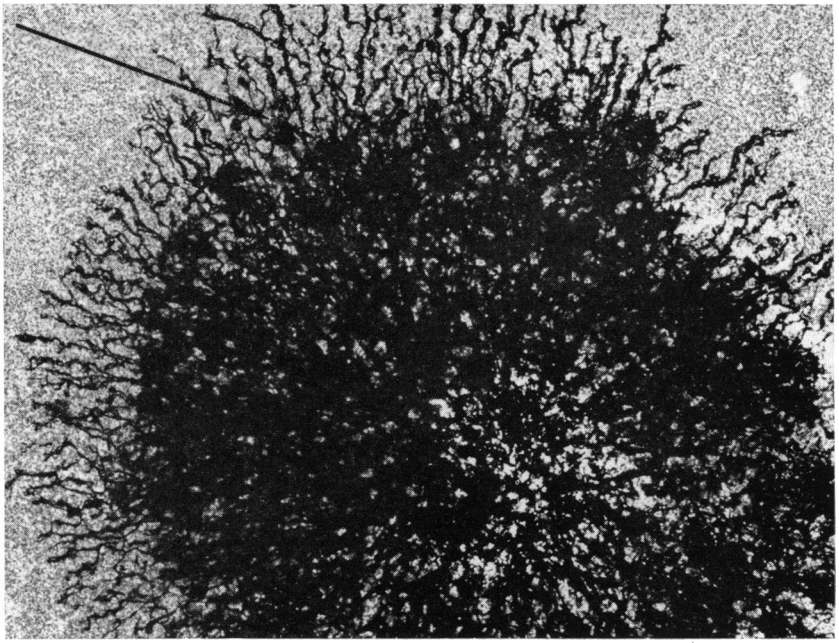


B

FIGURE 9

A, India-ink-injected flat retinal preparation from 21-day-old kitten raised in 80 per cent oxygen for six days, then in room air for fifteen days; note abnormal vascularization which extends only short distance from disk; compare with Figure 8. B, higher magnification of Figure 9A; arrow points to proliferating capillary tuft.

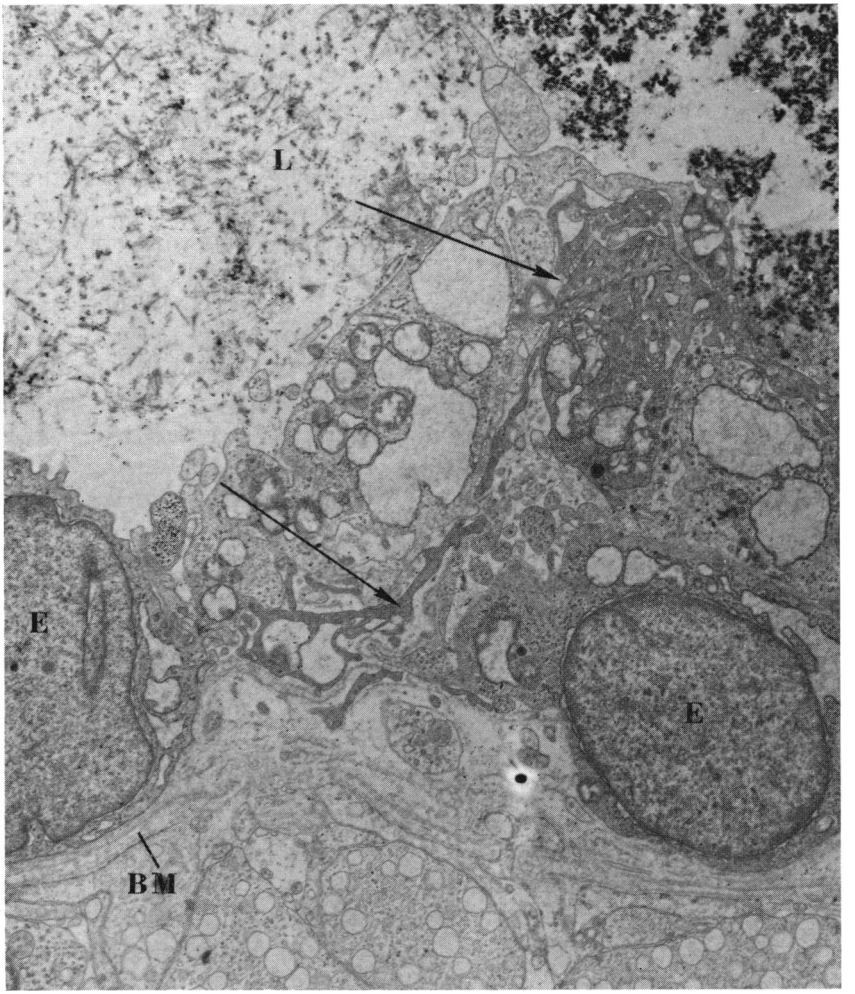


FIGURE 10

Section from 21-day-old kitten placed in 80 per cent oxygen for four days from the eleventh to fifteenth day of life, then removed to air for five days. L, lumen; BM, delicate basement membrane; E, endothelial nuclei. Note degenerative changes in endoplasmic reticulum (arrows). (Osmium fixation stained with lead citrate, magnification, 9,800; reduction factor, 1.5).

Ashton and co-workers,[74] that proliferation normally occurs only after oxygen vaso-obliteration is followed by lowering of the oxygen tension in the retina.

In 1953[77] Patz *et al.* were unable to produce abnormal retinal vaso-proliferation following hyperoxia in rats, although these lesions were

observed in mice, kittens, and puppies. In 1954[56] vasoproliferations were also detected in rats. Brands *et al.*[78] (1958) reported vasoproliferations in young rats subjected to oxygen. In 1960, in experiments to test histochemically for enzyme alteration in young rats treated with oxygen, we again found no evidence of abnormal vasoproliferative lesions in cross-sections. Ashton and Blach[79] (1961), reported no significant vasoproliferative lesions in either injected specimens or sections of young rats following hyperoxia. On reviewing our earlier studies we found that our rats were obtained from a colony maintained for several years at the Agriculture Research Center, Beltsville, Maryland. Fortunately this colony had been continued intact since our earlier studies. Four litters of these rats were obtained in 1963, raised in 80 per cent oxygen for five days, and then transferred to air for fifteen days. No instances of abnormal retinal proliferative lesions were observed. Our 1954 positive findings, therefore, were not confirmed, except by Brands. As a result we have discontinued the use of rats in RLF experiments.

Gerschman and co-workers[80] (1954) reported abnormal proliferation of the endothelium of the retinal vessels in mice exposed to hyperoxia. Michaelson *et al.*[81] found a delay in the formation of the capillary bed around the disk in mice subjected to hyperoxia. The vasoproliferative lesions of RLF were not observed; however, the lower concentrations of oxygen that were used may explain their results.

CURRENT STUDIES

Ophthalmoscopy in the young kitten is impossible due to the dense tunica vasculosa lentis and corneal haze. Mr. Robert W. Flower helped us develop an "artificial anterior chamber" for viewing the kitten retina through the microscope.[82] In applying the chamber to the eye the cornea and lens are removed. The optical principle is similar to that used in the earlier limbal window of Ashton and Cook[83] and in the cone device of Thuranszky.[84] The principal advantage of the artificial chamber is the precise control of the intraocular pressure during observation of the retinal vessels. Fluorescein angiography by still and motion picture photography has been utilized with the chamber (Figures 11–14).

Fluorescein angiography is a new means of studying the oxygen-induced changes in the immature retina and in combination with the artificial anterior chamber probably gives reliable physiological data for studying the retinal circulation. By utilization of high speed cinematography (64 frames per second), fluorescein flow through the

retinal vasculature can be studied in detail. Alterations in retinal flow can be analyzed in the standard projector at 16 frames per second, giving a 4 to 1 "slow motion" effect. Using the technique of Dollery,[85] it is possible with a single-frame movie projector (Kodak Analyst) to determine the velocity of blood flow in oxygen-treated and control animals. These methods are published in detail elsewhere.[86]

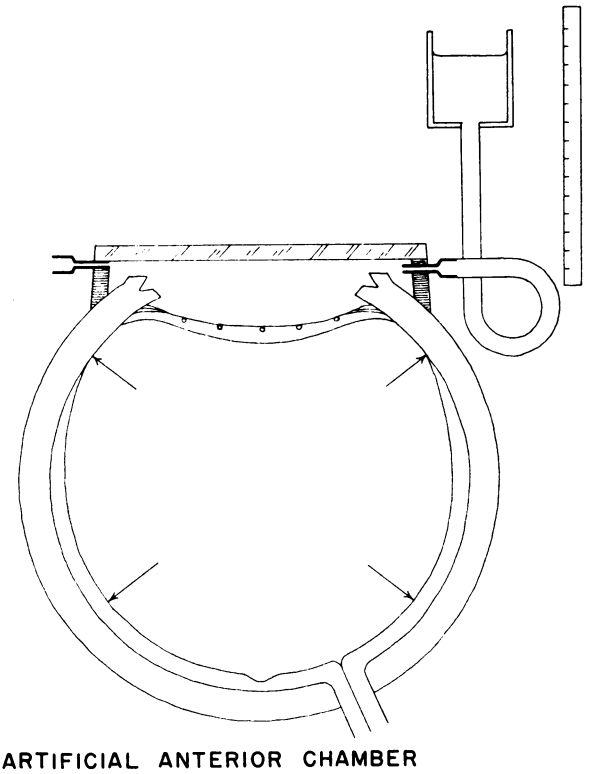


FIGURE 11

Schematic drawing of artificial anterior chamber. Lucite base of chamber is applied to sclera with Eastman 9-10 adhesive.

Fluorescein permits a study of the dynamic changes in the circulation produced by oxygen in the living subject and can be repeated within the time limitations of the experiment. Studies have been conducted with the chamber in place for up to six hours. We are planning, by gastric tube feeding and an improved temperature control unit,

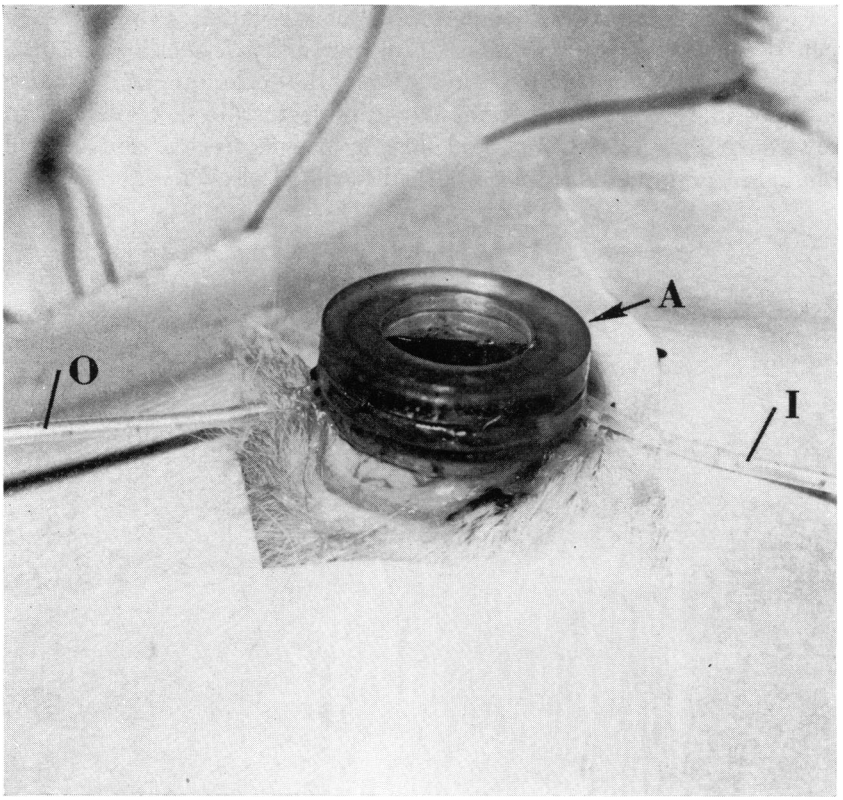


FIGURE 12
Artificial anterior chamber (A) in place on sclera; I, inflow tube; O, outflow tube.

to maintain the animal under light sedation for as long as twenty-four hours.

The primary goal in defining alterations in retinal vessel dynamics with fluorescein monitoring is to determine a consistent minimal and repeatable change that is produced by oxygen and relate it to simultaneous arterial pO_2 findings. Hopefully these data may be useful in establishing safer oxygen values for the premature infant. Fluorescein angiography gives a sharp definition of the capillary bed in the living animal and permits a more precise endpoint determination and quantitation of the degree of capillary closure than can be obtained with India ink injection. Ashton *et al.*[87] (1957), noting discrepancies between vessels injected with India ink and those visualized directly, stated that "these experiments demonstrated the danger of interpreting

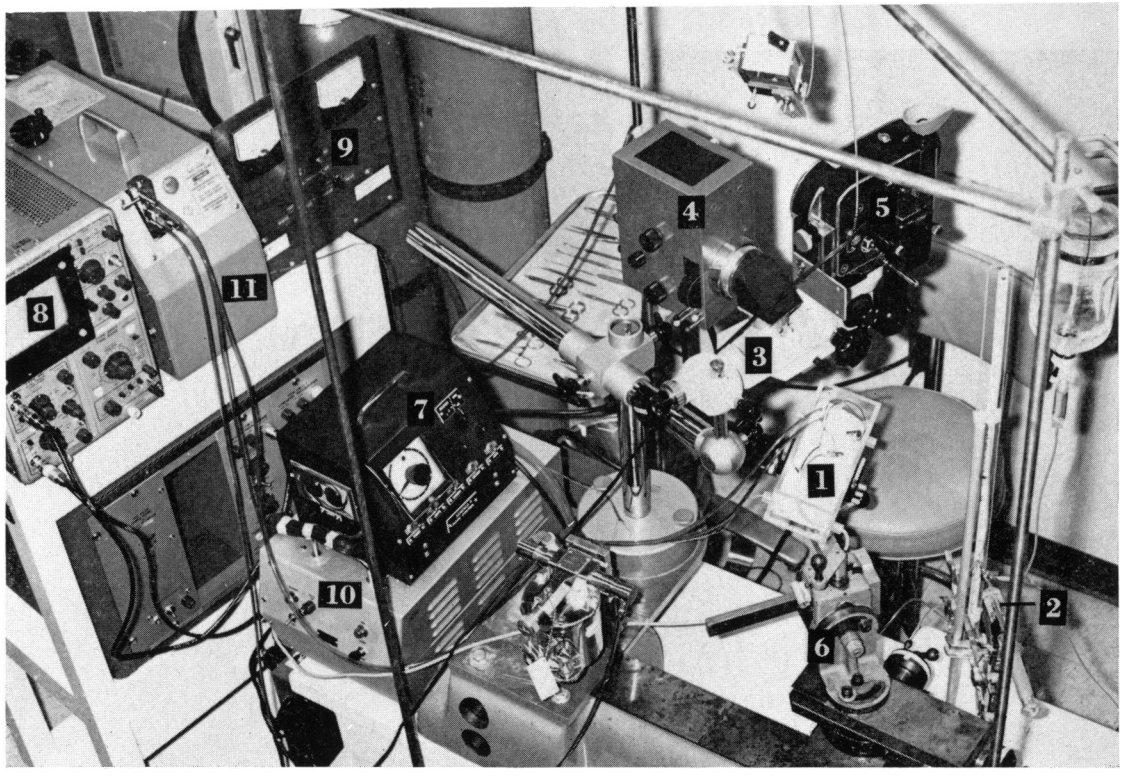


FIGURE 13

Instrumentation used to monitor retinal vessels in the living kitten through the artificial anterior chamber. 1. Plexiglass bed for supporting kitten. 2. Manometer assembly for controlling intraocular pressure. 3. Zeiss operating microscope. 4. Xenon light source. 5. Bolex motion picture camera in place over one eyepiece. 6. Micromanipulator lathe device. 7. Time-lapse control for movie camera. 8. Oscilloscope for EKG monitoring. 9. Electronic thermometer. 10. Power supply for lamp.

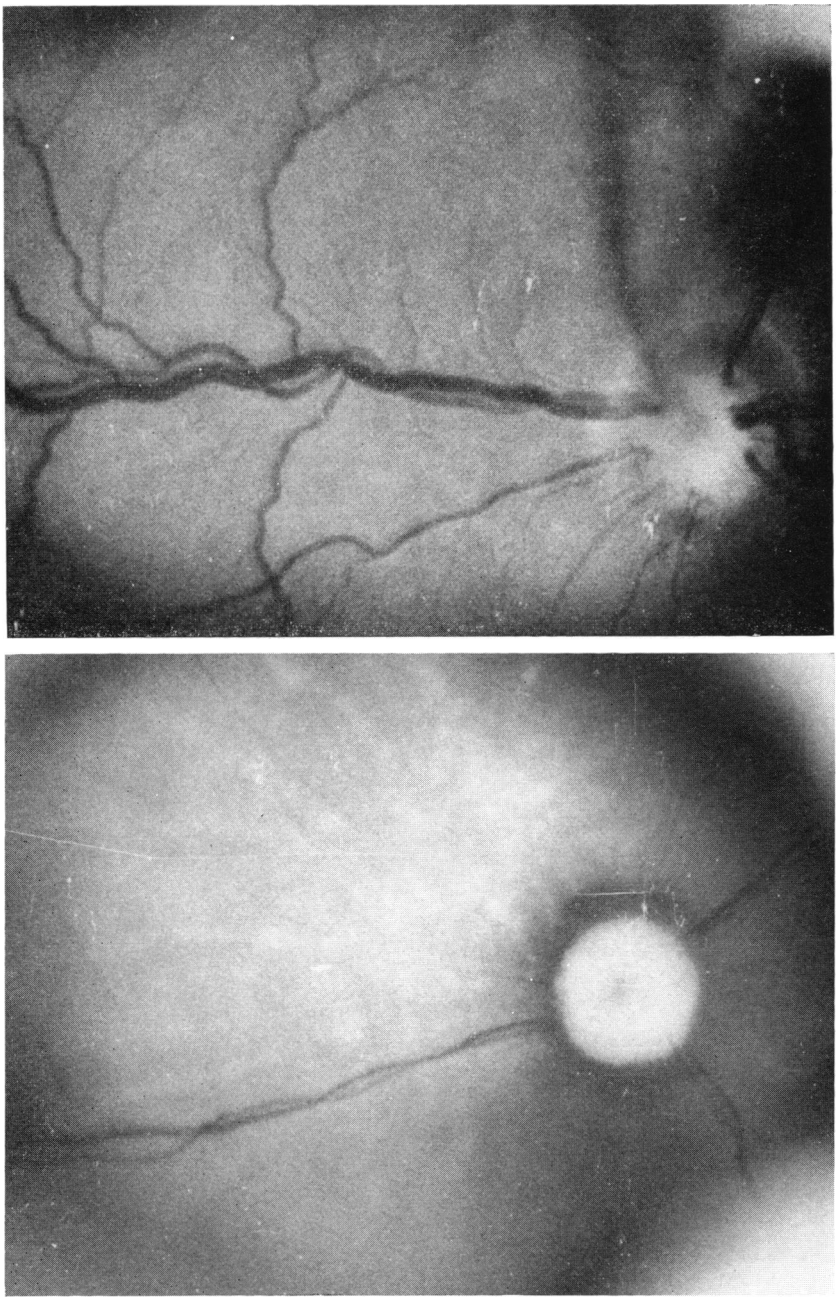


FIGURE 14

A, Retinal vessels seen through artificial anterior chamber in normal 14-day-old kitten (magnification, 25×). B, Litter mate to animal Figure 14A showing extreme degree of vasoconstriction of major vessels and obliteration of capillary bed and smaller branch vessels following 24 hours in 80 per cent oxygen.

India ink injection as a measure of vessel closure and again emphasized that the method should be used rather as a measure of the ability of the vessels to reopen."

In the interpretation of vessel caliber changes, it is significant that fluorescein usually shows the vessels to be slightly larger in diameter than they appear in routine photographs, apparently because of the plasma-skimming effect which causes the fluorescein to be visible in the periphery of the vessel lumen.

Fluorescein angiography permits a differentiation of the retinal and choroidal circulation *in vivo*. Experiments with prolonged hyperoxia, where retinal blood flow is completely shut off by oxygen vasoconstriction, can be accurately monitored with fluorescein angiography. In five kittens subjected to 72 hours of 80 per cent oxygen, complete cessation of retinal blood flow resulted (Figure 15). The demonstration of total cessation of retinal blood flow with an intact choroidal circulation simulates the clinical picture of central retinal arterial occlusion. In spite of the total absence of retinal blood flow, which can be objectively proved over a follow-up of four to five hours with the artificial chamber and fluorescein studies, light and electron microscopic examinations of the retina at the end of the experiment showed only insignificant damage to the nerve components of the retina. The choroid had essentially normal blood flow while breathing oxygen. By extending its normal diffusion range to the inner layers of the retina one might explain the relative preservation of nerve tissue. If this is correct, then we assume that blood-borne metabolites other than oxygen are not vital in the immediate ischemic effect. One other possibility, however, is that the immature retina of the kitten is relatively resistant to total ischemia. We plan to test this possibility by photocoagulating the retinal vessels at the disk through the chamber in young kittens breathing either room air or oxygen.

The secondary vasoproliferative phase following oxygen exposure has been studied by fluorescein cinematography with the artificial anterior chamber. Leakage from the areas of neovascularization occur. Apparently because of the continuous endothelium and tight endothelial junctions in normal retinal capillaries, fluorescein does not penetrate the capillary wall. Evidence of increased permeability of the abnormal vascular wall in the newly formed capillary tufts in areas of vasoproliferation was apparent as fluorescein pooled in the retina and vitreous in the areas of capillary proliferation (Figure 16). These oxygen-induced proliferations are quite similar to those seen in early proliferative diabetic retinopathy.

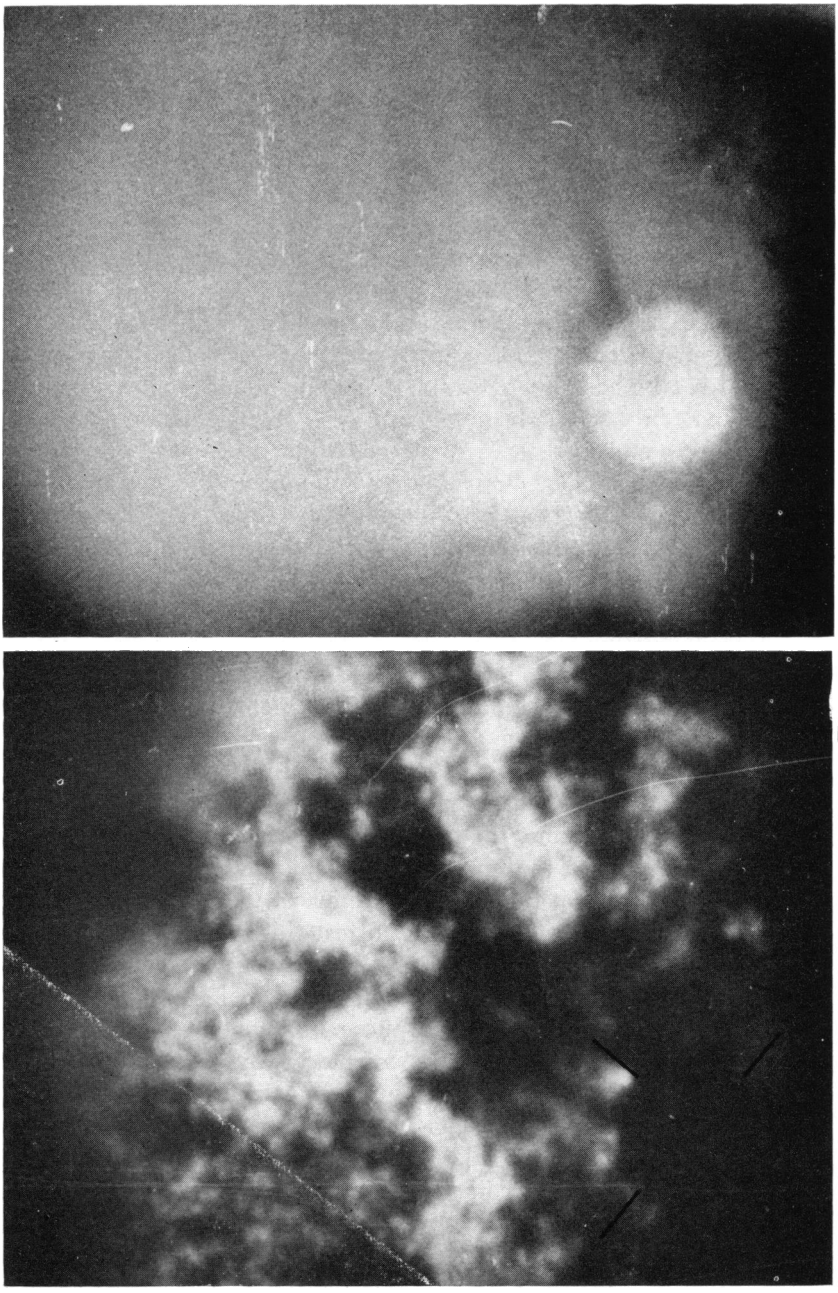
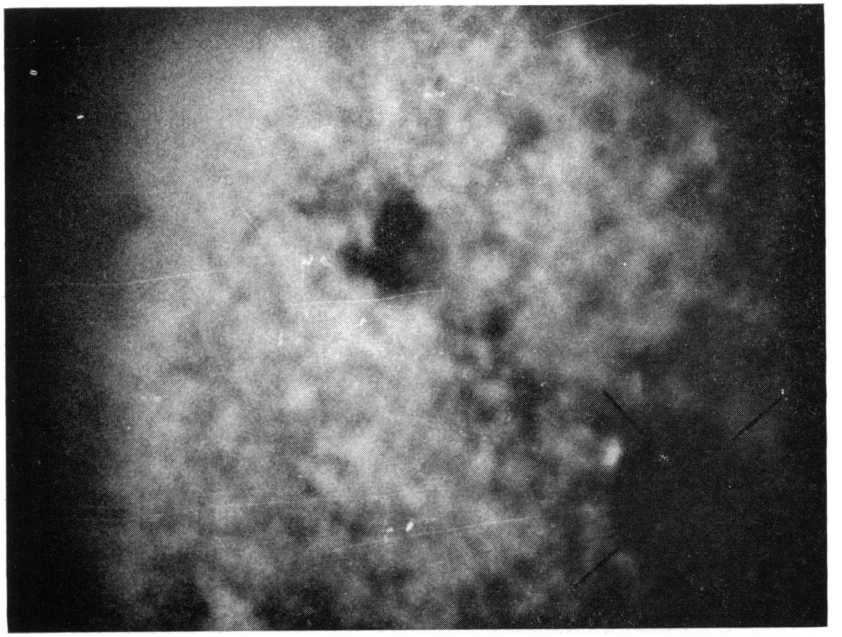


FIGURE 15

A, 14-day-old kitten placed in oxygen at 11 days of age continuously for 72 hours; note complete obliteration of entire retinal vascular bed (magnification, 25×). B, same animal as in Figure 15A following 72-hour oxygen exposure. After carotid injection, fluorescein is beginning to fill the choroidal vascular bed; arrows point to optic nerve.



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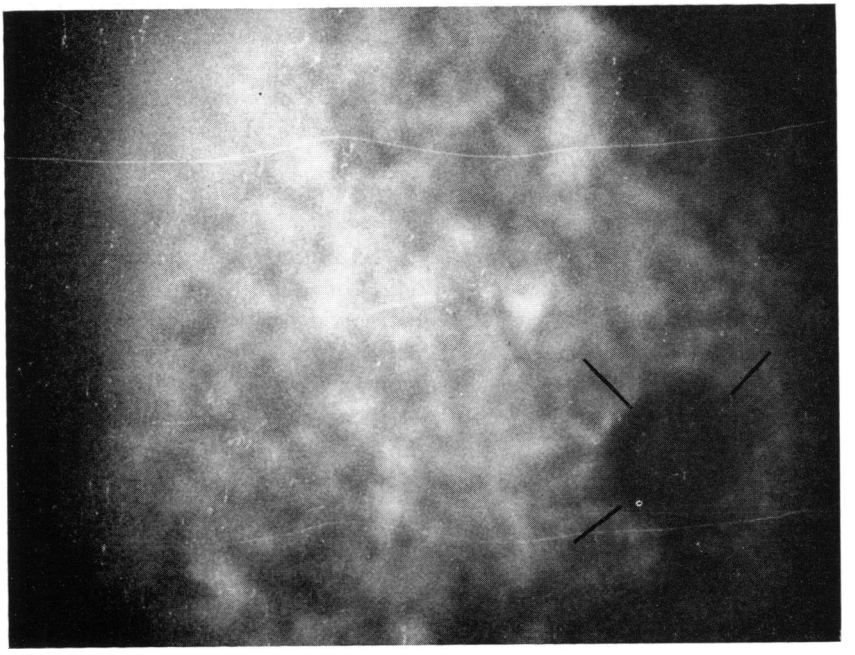


D

FIGURE 15 (Cont.)

C, one second after 15B showing further filling of choroid but with no filling of retinal vessels. D, three seconds after Figure 16A showing no filling of retinal vessels and good visualization of choroidal vascular bed with fluorescein.

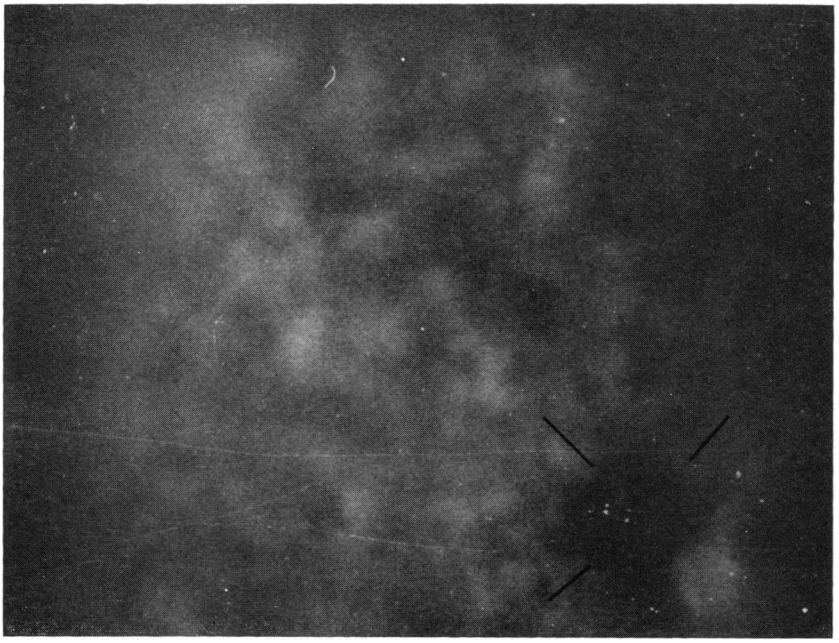


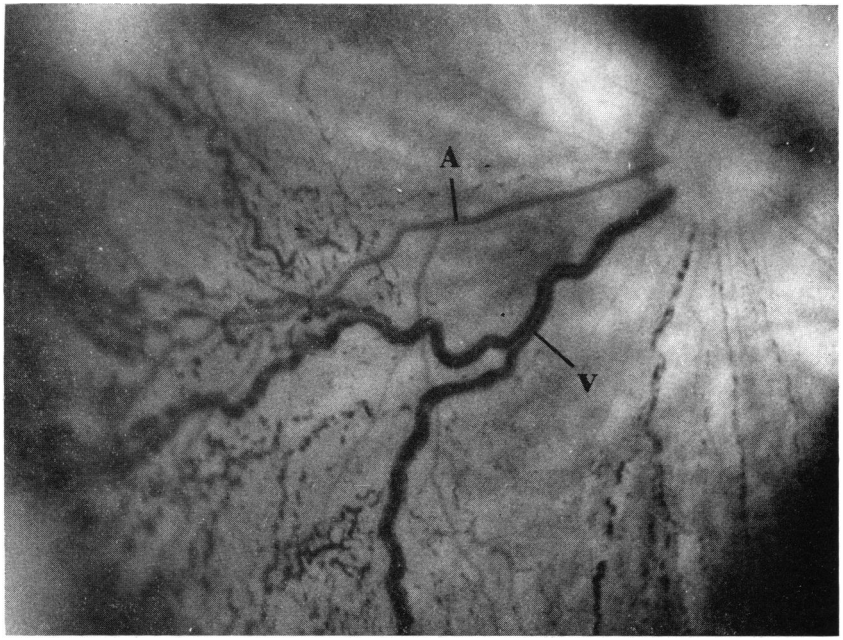
FIGURE 15 (Cont.)
E, eight seconds after photograph in Figure 16B. Fluorescein is emptying from choroidal bed but still no filling of retinal vessels.

Michelson *et al.*[88] recently found a marked reduction in retinal lactate by the Pasteur effect in kittens exposed to hyperoxia. Lactate was quantitatively measured by an enzymatic method. Although a similar degree of Pasteur effect was found in the adult retina, the greater capacity of the adult retina keeps lactic acid levels above the critical concentrations. These findings suggest that the level of lactic acid in the retina influences vasoconstriction and vasoproliferation. According to this theory, (1) vascular constriction and obliteration result from a depletion of retinal lactate by oxygen, and (2) after removal to room air of the vaso-obliterated retina, the retina becomes hypoxic, resulting in excess lactic acid accumulation. The excess lactic acid stimulates abnormal retinal vasoproliferation. The latter part of this theory is consistent with the observation by Imre[89] that intravitreal injections of lactic acid produced RLF-like vasoproliferations in the retinas of kittens. To test the first part of this theory we have perfused lactate through the artificial anterior chamber but thus far have noted no effect on oxygen-induced vasoconstriction. Experiments are in progress to test the effect of intravitreal lactate on vasoconstriction.

NEW CONCEPTS IN OXYGEN THERAPY

Oxygen therapy for premature infants is undergoing significant changes as pediatricians recognize the high mortality from pulmonary disease, especially the "idiopathic respiratory distress syndrome" or "hyaline membrane disease." In an epidemiological study in 1960 Avery and Oppenheimer[49] demonstrated a higher mortality in premature infants from 1954 to 1958 when oxygen was rigidly curtailed than in those from the previous period (1944–8) when it was used liberally. Although these investigators did not claim that oxygen curtailment was principally responsible for the higher mortality, it is significant that oxygen restriction was the chief difference in management of these two periods. Sutherland[90] (1962) reported similar findings in an independent survey. The studies of Strang and MacLeish[50] (1961), Warley and Gairdner[51] (1962), and Prod'ham *et al.*[52] (1965) have documented the severe oxygen deprivation in infants with the respiratory distress syndrome.

The "idiopathic respiratory distress syndrome" is the most common condition associated with respiratory failure in the premature infant. Most pediatricians estimate that approximately 10 per cent of all infants under 2500 gm birth weight are afflicted. In the United States, where approximately 400,000 infants under 2500 gm birth weight are born annually, approximately 10 per cent, or 40,000 will be afflicted. The exact cause of the syndrome is still unknown. However, clinical observations and careful animal experimentation suggest that diminished alveolar ventilation, gas transfer, and diminished pulmonary blood flow are involved. Impaired ventilation may occur from atelectasis and inadequate expansion of the lungs. Avery and Said[95] and Gruenwald[53] suggested that inadequate lung expansion may be associated with deficiencies in activity of surfactant. Abnormal pulmonary capillary permeability has also been suggested as an important factor based on the electron microscopic studies of Campiche *et al.*[91] (1961), who showed that the endothelial cells lining the capillaries were abnormally swollen in these infants. In the distress syndrome, pulmonary vasoconstriction and patency of the ductus arteriosus may be present and are accentuated by the hypoxic state. Diminished pulmonary blood flow results in lowered left atrial pressure so that the foramen ovale may remain patent causing further shunting or admixing of arterial and venous blood. A combination of these cardiopulmonary abnormalities deprives the respiratory distressed infant of an adequate oxygen supply to the tissues so that high concentrations of oxygen are required.



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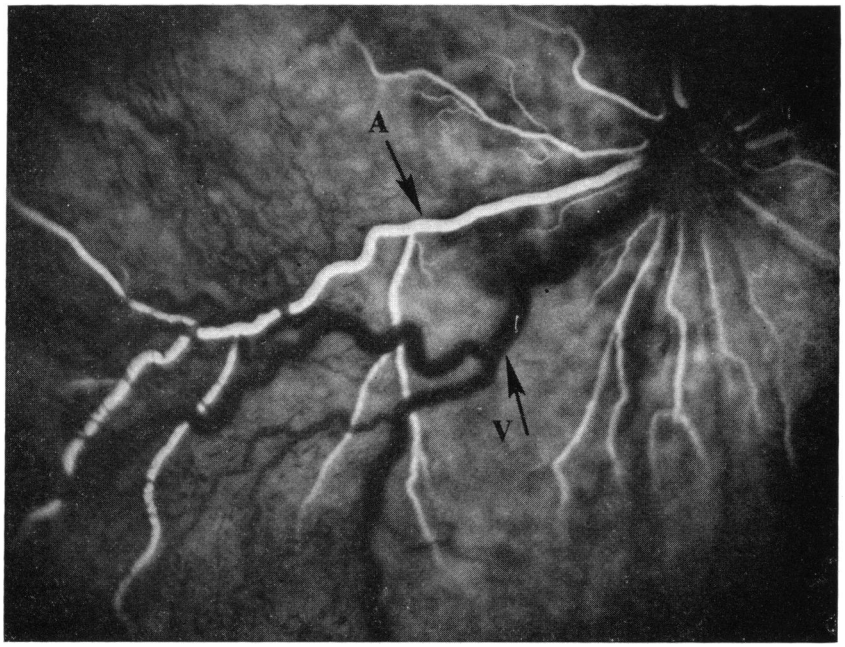
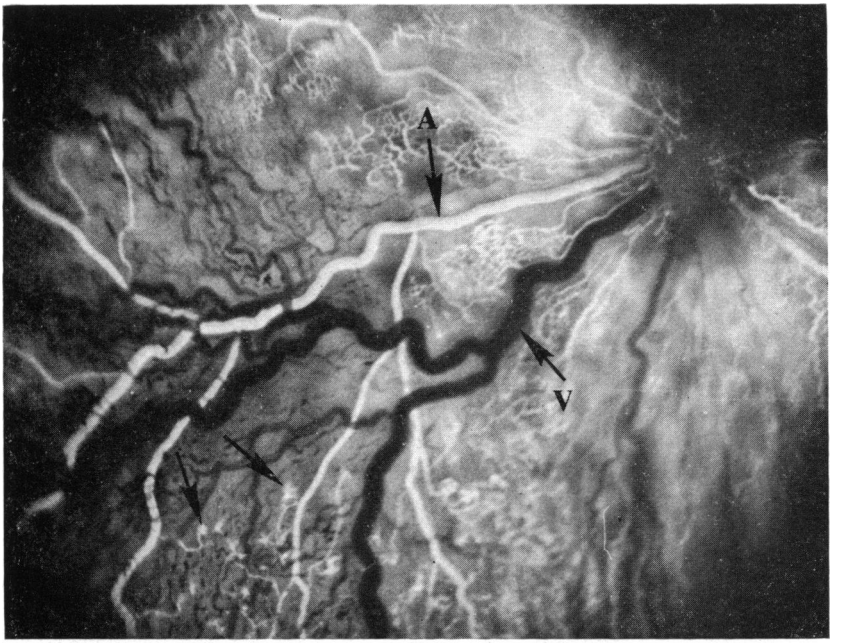


B

FIGURE 16

A, retinal vessels of kitten treated from tenth to twelfth day of age in 80 per cent oxygen and removed to room air for seven days; note marked dilatation and tortuosity of larger retinal vessels and abnormality of capillary bed; A, artery, V, vein. B, same animal as in Figure 16A showing arterial phase of fluorescein filling retinal vessels.



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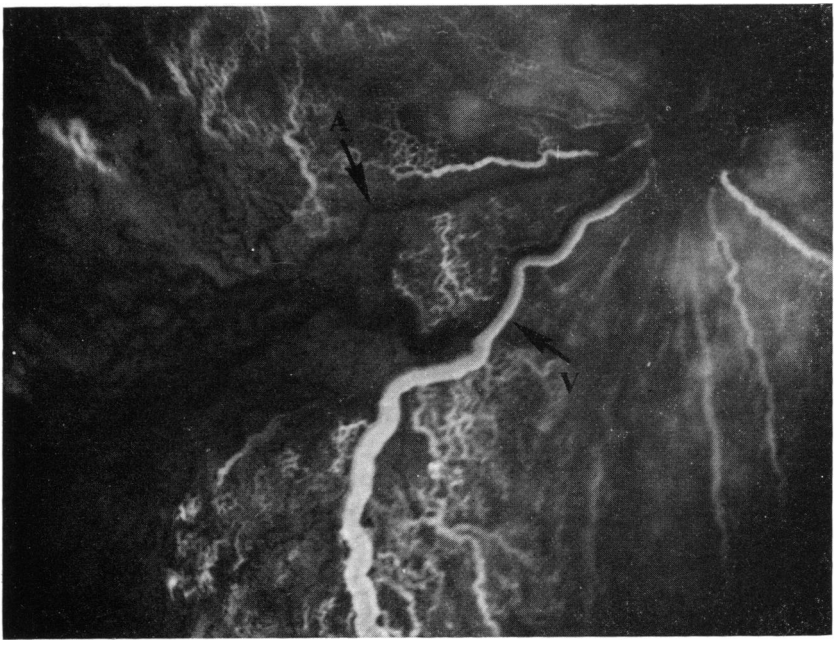

D

FIGURE 16 (Cont.)

C, eight seconds after photograph in Figure 16B; arrows point to delicate tufts of neovascularization. D, one second after Figure 16C showing filling of the venous side of the capillary bed; note laminar flow in veins.

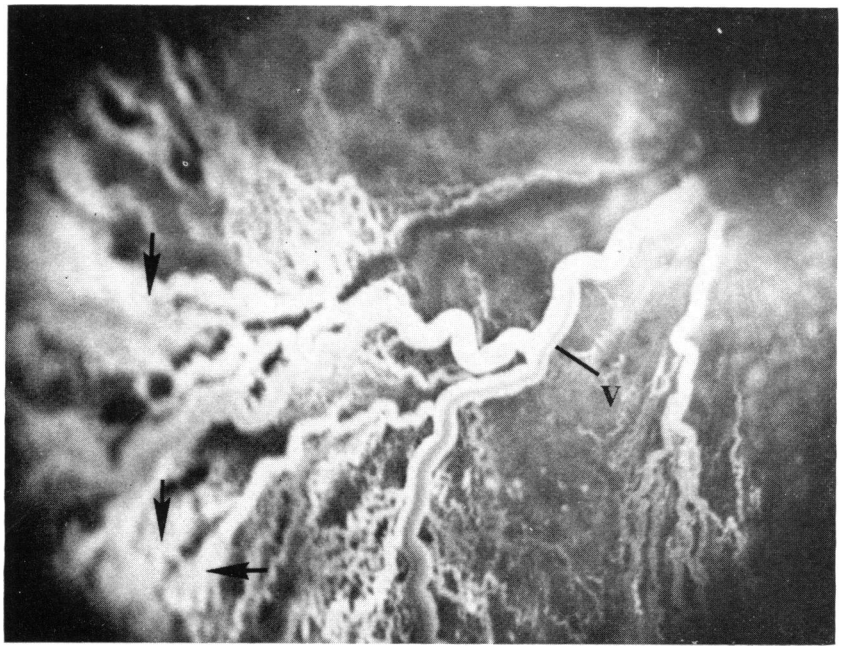

FIGURE 16 (Cont.)
E, three seconds after Figure 16D showing late venous filling and delayed emptying of the major veins. Note leakage of fluorescein from vessels in periphery of field (arrows).

It is significant that the pulmonary artery, in contrast to the cerebral or retinal vessels, actively constricts under the stimulus of hypoxia and hypercapnea. Klaus and Meyer[92] have suggested that the use of high concentrations of oxygen for short periods of time in the early neonatal period to produce pulmonary vasodilatation might prevent or abort the respiratory distress syndrome. A typical example of arterial oxygen levels (pO_2) that may be found in a normal infant when compared with one suffering from the respiratory distress syndrome is cited in Table 1. The distress syndrome infant in this instance requires 80 per cent oxygen to achieve the same arterial pO_2 level as the normal infant breathing room air.

NEW ROLE OF OPHTHALMOSCOPY

Klaus and Meyer[92] (1966) state that infants with the respiratory distress syndrome may frequently require high concentrations of

TABLE 1. INCUBATOR OXYGEN CONCENTRATION AND ARTERIAL PO_2

	20% O_2	40% O_2	80% O_2
Normal infant	85 mm	160 mm	320 mm
Respiratory distress	35 mm	50 mm	85 mm

oxygen for several days after birth. As long as the cardiopulmonary deficiencies persist in these infants, probably no real danger to their eyes exists. The cardiopulmonary deficiencies, however, may disappear at any time. If that infant is then breathing high concentrations of oxygen, the arterial pO_2 will rise and possibly reach levels toxic to the retina. Ashton[93] (1964) and Patz[55] (1967) have stated that it is apparently the sustained high arterial pO_2 level that damages the retina and not the ambient concentration of oxygen in the incubator.

Frequent monitoring of arterial blood oxygen levels provides a means of avoiding potentially retinotoxic arterial oxygen levels. At the present time, however, there are no data available on the precise arterial pO_2 values that cause retinal damage. Studies are in progress in our nursery in collaboration with Dr. Mary Ellen Avery to document photographically retinal vessel caliber in relation to arterial pO_2 sampling. These values will be evaluated over a two-year period and they will be correlated with initial and later ophthalmoscopic findings in these infants.

Obtaining frequent arterial oxygen gas measurements can be a formidable procedure in many institutions. The technique of arterial sampling requires a highly skilled pediatric team and the blood oxygen analysis needs specially trained personnel and expensive instrumentation. For these reasons only a few hospitals are equipped today to monitor arterial oxygen tension. In the vast majority of hospitals, infants with the distress syndrome will receive oxygen therapy without arterial gas monitoring. For these infants cyanosis is the usual indication for added oxygen. Using cyanosis as an indicator for oxygen therapy, however, presents a serious problem. Figure 17 demonstrates that the quantity of oxygen bound to hemoglobin (per cent saturation) is dependent upon the partial pressure of oxygen (pO_2). Cyanosis is observed when hemoglobin saturation is below approximately 80 per cent. Hemoglobin saturation and pO_2 levels are fairly linear below 80 per cent saturation; however, the flattening of the S-shaped dissociation curve above 90 per cent saturation makes it impossible to monitor blood oxygen tension by observing oxygen saturation. Since the per

cent hemoglobin saturation with oxygen determines the color of the blood, the infant will be pink at 90 per cent saturation with an arterial pO_2 of 70 mm and show little change in color with a pO_2 of 400 mm. The desirability of monitoring arterial blood pO_2 levels directly to avoid retinal damage is therefore obvious.

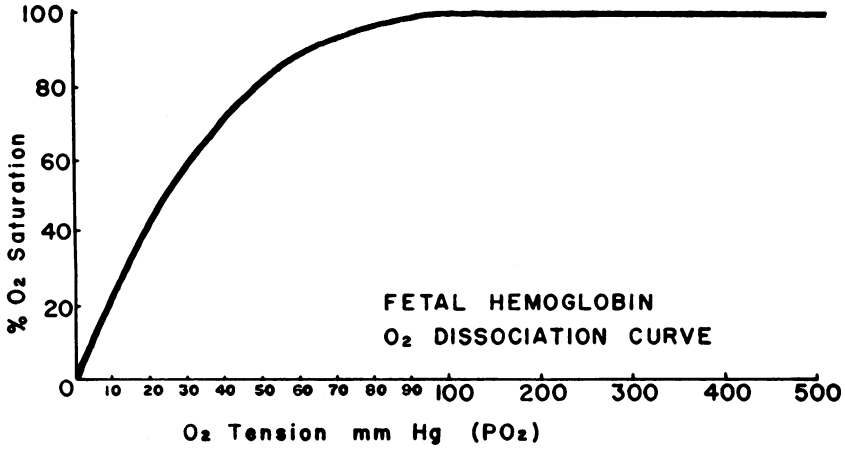

FIGURE 17

Oxygen dissociation curve for hemoglobin in the premature infant. Note that when the saturation curve flattens, the arterial saturation changes only insignificantly as the arterial pO_2 rises.

Since in the majority of hospitals arterial oxygen monitoring is not readily available, ophthalmoscopy may serve as a useful method to avoid retinotoxic levels of oxygen. Examination of the retina for retinal vasoconstriction can provide a general guideline to the arterial oxygen levels that have been maintained. Since the retina is the main area of concern during excessive arterial pO_2 levels, ophthalmoscopy should be performed, where feasible, whenever the premature infant receives prolonged high concentrations of oxygen. If the blood level has been excessive, the premature retina will generally show a proportionate degree of vasospasm. The constricted retinal vessels may gradually open during ophthalmoscopy so that 10 to 15 minutes after removal of the infant from the incubator the vessels are nearly normal in caliber. Here, if the incubator oxygen level is promptly reduced, permanent retinal damage probably will be avoided. If severe retinal vasospasm persists 15 to 20 minutes after removal from the incubator

to room air, one can predict that some degree of retrolental fibroplasia may develop. The incubator oxygen concentration should be promptly lowered to minimize any further retinal vascular damage. If the retinal vessels are normal in caliber, one can estimate that safe arterial oxygen levels probably have not been exceeded. These are only general guidelines and obviously minimal changes in the retinal vessels or changes limited to the periphery may be overlooked.

Patz *et al.*[41] observed severe retinal vasoconstriction in the first few premature infants placed in high oxygen in early 1951, implicating the retinal vasoconstrictive response to hyperoxia in the possible genesis of retrolental fibroplasia. Attenuation of the retinal vessels in infants receiving excess oxygen has been observed in other nurseries. Huggert[58] (1953) stated that four out of eight cases in his nursery who later developed classical RLF showed "vessels narrow as threads." In his subsequent studies Huggert[59] (1954), discussing two patients with RLF, stated that "during the whole of the time that oxygen was being administered one observed these narrow vessels. In both cases the abnormal increase in the width of the vessels was noticed at the first examination that was made after the administration of oxygen had been discontinued which in both cases was three days after the continuous oxygen therapy had been stopped." He also reported that in other infants in whom cicatricial RLF did not develop the vessels were extremely constricted during oxygen therapy and within a few days after return to air the vessels resumed normal caliber or became dilated. LaMotte[94] (1951) recorded cases in which extreme narrowing of the vessels was recorded prior to the later dilatation phase of RLF. The objectivity of these clinical observations is enhanced by their being recorded prior to the demonstration of vasoconstriction and obliteration in animals and without knowledge of any expected change in vessel caliber. They demonstrate the feasibility of recognizing ophthalmoscopically severe vasoconstriction as an index of overoxygenation (Figure 18).

Ophthalmoscopy may be difficult, however, in the very small, premature infant. Infants with birth weights under 1500 gm usually have a slight vitreous haze. This haze combined with remnants of the tunica vasculosa lentis that are still present can interfere with direct ophthalmoscopy during the first few days of life. With the indirect ophthalmoscope and the use of a small, self-retaining lid speculum, adequate visualization can be obtained in many instances. Infants between 1500 and 2500 gm birth weight who require large amounts of oxygen can

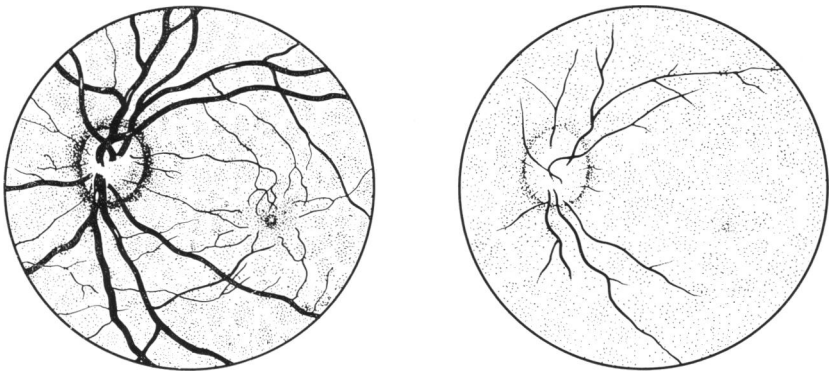

FIGURE 18

Artist's drawing of severe vasoconstriction in a premature infant exposed to 70 per cent oxygen for four days in our original nursery study (right). Normal retinal vessels are sketched on left for comparison.

generally be studied adequately from birth either by direct or indirect ophthalmoscopy (Figure 19).

We have found that, where the infant cannot be removed from the Isolette type of incubator, indirect ophthalmoscopy can be readily performed through the wall of the incubator. Here the examiner introduces the hand-held lens through the sleeves of the incubator and views directly through the plexiglass wall (Figure 19).

Until methods for measuring arterial oxygen tension become universally available, ophthalmoscopic monitoring of retinal vessel caliber is recommended. The following general suggestions on oxygen therapy are offered:

1. Oxygen should be administered to the premature infant only where hypoxia is clearly demonstrated or strongly suspected.

2. When high concentrations of oxygen are required for significant periods in additon to measuring the incubator oxygen level, arterial oxygen tension monitoring is recommended where facilities are available.

3. Severe retinal vasoconstriction can be in many cases an indicator of possible oxygen overuse; therefore, monitoring of the eyegrounds at occasional intervals is recommended as an additional safeguard in therapy. When marked constriction is detected, prompt reduction in the concentration of administered oxygen may prevent retinal damage.

4. Since the retina of the full-term infant is incompletely vascularized temporally, oxygen therapy should be cautiously administered and limited to specific clinical indications.

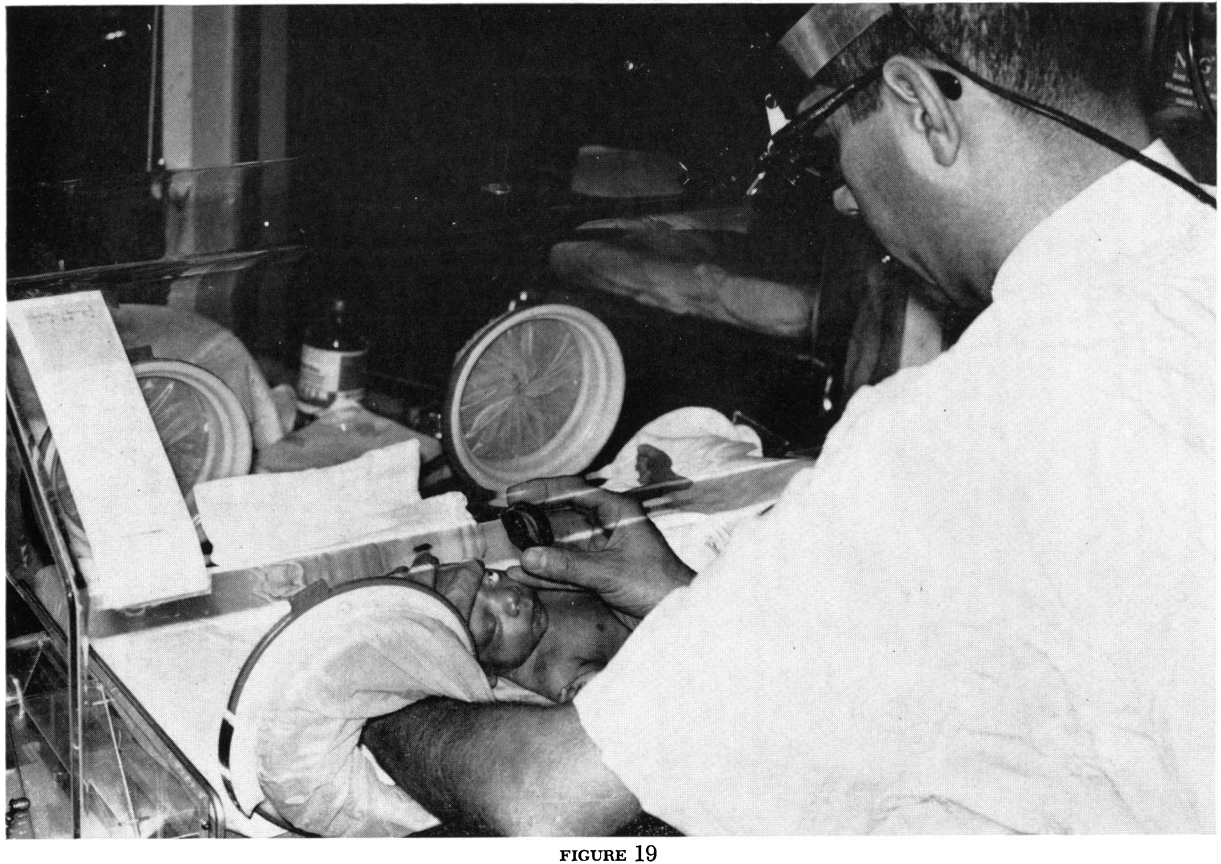

FIGURE 19

Indirect ophthalmoscopy performed through plexiglass wall of incubator. Examiner introduces hand-held lens through porthole sleeves.

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